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A METHOD USING A 1	FOR ISOLATING A POLYNUC BAC-BASED DNA LIBRARY. AP: (s) For DO/EO/US:	LEOTIDE OF INTEREST FROM THE PLICATION TO THE DETECTION OF	MYCOBACTERIA			
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3. []	This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).					
4. [X]	A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.					
5. 🚊 [X]	A copy of the Internati	onal Application as filed (39	5 U.S.C. 371(c)(2))			
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Ernest F. Chapman / Reg. No. 25,961

Submitted: October 16, 2000

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A METHOD FOR ISOLATING A POLYNUCLEOTIDE OF INTEREST FROM THE GENOME OF A MYCOBACTERIUM USING A BAC-BASED DNA LIBRARY. APPLICATION TO THE DETECTION OF MYCOBACTERIA.

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## I. Background of the invention

The present invention pertains to a method for isolating a polynucleotide of interest that is present in the genome of a mycobacterium strain and/or is expressed by said mycobacterium strain and that is absent or altered in the genome of a different mycobacterium strain and/or is not expressed in said different mycobacterium strain, said method comprising the use of at least one clone belonging to a genomic DNA library of a given mycobaterium strain, said DNA library being cloned in a bacterial artificial chromosome (BAC). The invention concerns also polynucleotides identified by the above method, as well as detection methods for mycobacteria, particularly Mycobacterium tuberculosis, and kits using said polynucleotides as primers or probes. Finally, the invention deals with BAC-based mycobacterium DNA libraries used in the method according to the invention and particularly BAC-based Mycobacterium tuberculosis and Mycobacterium bovis BCG DNA libraries.

Radical measures are required to prevent the grim predictions of the World Health Organisation for the evolution of the global tuberculosis epidemic in the next century becoming a tragic reality. The powerful combination of genomics and bioinformatics is providing a wealth of information about the etiologic agent, Mycobacterium tuberculosis, that will facilitate the conception and development of new therapies. The start point for genome sequencing was the integrated map of the 4.4 Mb circular chromosome of the widely-used, virulent reference strain, M. tuberculosis H37Rv and appropriate cosmids were subjected to systematic shotgun sequence analysis at the Sanger Centre.

Cosmid clones (Balasubramanian et al., 1996; Pavelka et al., 1996) have played a crucial role in the M. tuberculosis H37Rv genome sequencing project. However, problems such as under-representation of certain regions of the chromosome, unstable inserts and the relatively small insert size complicated the production of a comprehensive set of canonical cosmids representing the entire genome.

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### II. Summary of the invention

In order to avoid the numerous technical constraints encountered in the state of the art, as decribed hereabove, when using genomic mycobacterial DNA libraries constructed in cosmid clones, the inventors have attempted to realize genomic mycobacterial DNA libraries in an alternative type of vectors, namely Bacterial Artificial Chromosome (BAC) vectors.

The success of this approach depended on whether the resulting BAC clones could maintain large mycobacterial DNA inserts. There are various reports describing the successful construction of a BAC library for eucaryotic organisms (Cai et al., 1995; Kim et al., 1996; Misumi et al., 1997; Woo et al., 1994; Zimmer et al., 1997) where inserts up to 725 kb (Zimmer et al., 1997) were cloned and stably maintained in the *E. coli* host strain.

Here, it is shown that, surprisingly, the BAC system can also be used for mycobacterial DNA, as 70% of the clones contained inserts in the size of 25 to 104 kb.

This is the first time that bacterial, and specifically mycobacterial, DNA is cloned in such BAC vectors.

In an attempt to obtain complete coverage of the genome with a minimal overlapping set of clones, a Bacterial Artificial Chromosome (BAC) library of *M. tuberculosis* was constructed, using the vector pBeloBAC11 (Kim et al., 1996) which combines a simple phenotypic screen for recombinant clones with the stable propagation of large inserts (Shizuya et al., 1992). The BAC cloning system is based on the *E. coli* F-factor, whose replication is strictly controlled and thus ensures stable maintenance of large constructs (Willets et al., 1987). BACs have been widely used for cloning of DNA from various eucaryotic species (Cai et al., 1995; Kim et al., 1996; Misumi et al., 1997; Woo et al., 1994; Zimmer et al., 1997). In contrast, to our knowledge this report describes the first attempt to use the BAC system for cloning bacterial DNA.

A central advantage of the BAC cloning system over cosmid vectors used in prior art is that the F-plasmid is present in only one or a maximum of two copies per cell, reducing the potential for recombination between DNA fragments and, more importantly, avoiding the lethal overexpression of cloned bacterial genes. However, the presence of the BAC as just a single copy means that plasmid DNA has to be extracted from a large volume of culture to obtain

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sufficient DNA for sequencing and it is described here in the examples a simplified protocol to achieve this.

Further, the stability and fidelity of maintenance of the clones in the BAC library represent ideal characteristics for the identification of genomic differences possibly responsible for phenotypic variations in different mycobacterial species.

As it will be shown herein, BACs can be allied with conventional hybridization techniques for refined analyses of genomes and transcriptional activity from different mycobacterial species.

Having established a reliable procedure to screen for genomic polymorphisms, it is now possible to conduct these comparisons on a more systematic basis than in prior art using representative BACs throughout the chromosome and genomic DNA from a variety of mycobacterial species.

As another approach to display genomic polymorphisms, the inventors have also started to use selected H37Rv BACs for "molecular combing" experiments in combination with fluorescent *in situ* hybridization (Bensimon et al., 1994; Michalet et al., 1997). With such techniques the one skilled in the art is enabled to explore the genome of mycobacteria in general and of *M. tuberculosis* in particular for further polymorphic regions.

The availability of BAC-based genomic mycobacterial DNA libraries constructed by the inventors have allowed them to design methods and means both useful to identify genomic regions of interest of pathogenic mycobacteria, such as *Mycobacterium tuberculosis*, that have no counterpart in the corresponding non-pathogenic strains, such as *Mycobacterium bovis* BCG, and useful to detect the presence of polynucleotides belonging to a specific mycobacterium strain in a biological sample.

By a biological sample according to the present invention, it is notably intended a biological fluid, such as plasma, blood, urine or saliva, or a tissue, such as a biopsy.

Thus, a first object of the invention consists of a method for isolating a polynucleotide of interest that is present in the genome of a mycobacterium strain and/or is expressed by said mycobacterium strain and that is absent or altered in the genome of a different mycobacterium strain and/or is not expressed in said different mycobacterium strain, said method comprising the use of at least one clone belonging to a genomic DNA library of a given mycobaterium strain, said DNA library being cloned in a bacterial artificial chromosome (BAC).

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The invention is also directed to a polynucleotide of interest that has been isolated according to the above method and in partoular a polynucleotide containing one or several Open Reading Frames (ORFs), for example ORFs encoding either a polypeptide involved in the pathogenicity of a mycobacterium strain or ORFs encoding Polymorphic Glycine Rich Sequences (PGRS).

Such polynucleotides of interest may serve as probes or primers in order to detect the presence of a specific myobacterium strain in a biological sample or to detect the expression of specific genes in a particular mycobacterial strain of interest.

The BAC-based genomic mycobacterial DNA libraries generated by the present inventors are also part of the invention, as well as each of the recombinant BAC clones and the DNA insert contained in each of said recombinant BAC clones.

The invention also pertains to methods and kits for detecting a specific mycobacterium in a biological sample using either at least one recombinant BAC clone or at least one polynucleotide according to the invention, as well as to methods and kits to detect the expression of one or several specific genes of a given mycobacterial strain present in a biological sample.

# 20 III. Brief description of the Figures.

In order to better understand the present invention, reference will be made to the appended figures which depicted specific embodiments to which the present invention is in no case limited in scope with.

- Figures 1A and 1B: PCR-screening for unique BAC clones with specific primers for 2 selected genomic regions of the H37Rv chromosome, using 21 pools representating 2016 BACs (Figure 1A) and sets of 20 subpools from selected positive pools (Figure 1B).
- Figure 2: Pulsed-field gel electrophoresis gel of *Dra*I- cleaved BAC clones used for estimating the insert sizes of BACs.
  - Figure 3: Minimal overlapping BAC map of *M. tuberculosis* H37Rv superimposed on the integrated physical and genetic map established by Philipp et al. (18). Y- and I- numbers show pYUB328 (2) and pYUB412 (16) cosmids which were shotgun sequenced during the H37Rv genome sequencing project. Y-cosmids marked with \* were shown in the integrated physical and genetic map

- (18). Rv numbers show the position of representative BAC clones relative to sequenced Y- and I- clones. Squared Rv numbers show BACs which were shotgun sequenced at the Sanger Centre.
- Figures 4A and 4B: Ethidium bromide stained gel (Figure 4A) and corresponding Southern blot (Figure 4B) of *Eco*RI and *Pvu*II digested Rv58 DNA hybridized with <sup>32</sup>P labeled genomic DNA preparations from *M. tuberculosis* H37Rv, *M. bovis* ATCC 19210 and *M. bovis* BCG Pasteur.
- Figure 5: Organisation of the ORFs in the 12.7 kb genomic region present in M. tuberculosis H37Rv but not present in M. bovis ATCC 19210 and M. bovis BCG
- Positions of EcoRI and PvuII restriction sites are shown. Vertical dashes represent stop codons. The 11 ORFs correspond to the ORFs MTCY277.28 to MTCY277.38 / accession number Z79701 -EMBL Nucleotide Sequence Data Library. The junction sequences flanking the polymorphic region are shown.
- Figure 6: Variation in the C-terminal part of a PE-PGRS open reading frame in M. tuberculosis strain H37Rv relative to M. bovis BCG strain Pasteur.
  - The numbers on the right side of the Figure denote the position of the end nucleotides, taking as the reference the *M. tuberculosis* genome.
- Figure 7: Polynucleotide sequence next to the HindIII cloning site in the BAC vector pBeloBAC11 (Kim et al., 1996) used to clone the inserts of the BAC-based myobacterial genomic DNA library according to the invention.
  - NotI: location of the NotI restriction sites.
  - Primer T7-BAC1: nucleotide region recognized by the T7-BAC1 primer shown in Table 1.
- T7 promoter: location of the T7 promoter region on the pBeloBac11 vector.

  Primer T7-Belo2: nucleotide region recognized by the T7-Belo2 pimer shown in Table 1.
  - Hind III: the HindIII cloning site used to clone the genomic inserts in the pBeloBAC11 vector.
- 30 SP6-Mid primer: nucleotide region recognized by the SP6 Mid primer shown in Table 1.
  - SP6-BAC1 primer: nucleotide region recognized by the SP6 BAC1 primer shown in Table 1.
  - SP6 promoter: location of the SP6 promoter region on the pBeloBac11 vector.

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# IV. Detailed description of the preferred embodiments.

As already mentioned hereinbefore, the present invention is directed to a method for isolating a polynucleotide of interest that is present in the genome of a mycobacterium strain and/or is expressed by said mycobacterium strain and that is absent or altered in the genome of a different mycobacterium strain and/or is not expressed in said different mycobacterium strain, said method comprising the use of at least one clone belonging to a genomic DNA library of a given mycobaterium strain, said DNA library being cloned in a bacterial artificial chromosome (BAC) type vector.

For this purpose, the inventors have constructed several BAC-based mycobacterial genomic DNA libraries that may be used in order to perform the above described method.

Because it is the first time that mycobacterial genomic DNA has been successfully cloned in BAC type vectors, and because these DNA libraries are then novel and nonobvious, an object of the present invention consists in a myobacterial genomic DNA library cloned in such a BAC type vector.

As an illustrative example, a BAC-based DNA library of Mycobacterium tuberculosis has been realized. Forty-seven cosmids chosen from the integrated map of the 4.4 Mb circular chromosome (Philipp et al., 1996a) were shotgunsequenced during the initial phase of the H37Rv genome sequence project. The sequences of these clones were used as landmarks in the construction of a minimally overlapping BAC map. Comparison of the sequence data from the termini of 420 BAC clones allowed us to establish a minimal overlapping BAC map and to fill in the existing gaps between the sequence of cosmids. As well as using the BAC library for genomic mapping and sequencing, we also tested the system in comparative genomic experiments in order to uncover differences between two closely related mycobacterial species. As shown in a previous study (Philipp et al., 1996b), M. tuberculosis, M. bovis and M. bovis BCG, specifically BCG Pasteur strain, exhibit a high level of global genomic conservation, but certain polymorphic regions were also detected. Therefore, it was of great interest to find a reliable, easy and rapid way to exactly localize polymorphic regions in mycobacterial genomes using selected BAC clones. This approach was validated by determining the exact size and location of the polymorphisms in the genomic region of DraI fragment Z4 (Philipp et al., 1996b), taking advantage of the availability of an appropriate BAC clone covering the polymorphic region and

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the H37Rv genome sequence data. This region is located approximately 1.7 Mb from the origin of replication.

The Bacterial Artificial Chromosome (BAC) cloning system is capable of stably propagating large, complex DNA inserts in Escherichia coli. As part of the Mycobacterium tuberculosis H37Rv genome sequencing project, a BAC library was constructed in the pBeloBAC11 vector and used for genome mapping, confirmation of sequence assembly, and sequencing. The library contains about 5000 BAC clones, with inserts ranging in size from 25 to 104 kb, representing theoretically a 70 fold coverage of the M. tuberculosis genome (4.4 Mb). A total of 840 sequences from the T7 and SP6 termini of 420 BACs were determined and compared to those of a partial genomic database. These sequences showed excellent correlation between the estimated sizes and positions of the BAC clones and the sizes and positions of previously sequenced cosmids and the resulting contigs. Many BAC clones represent linking clones between sequenced cosmids, allowing full coverage of the H37Rv chromosome, and they are now being shotgun-sequenced in the framework of the H37Rv sequencing project. Also, no chimeric, deleted or rearranged BAC clones were detected, which was of major importance for the correct mapping and assembly of the H37Rv sequence. The minimal overlapping set contains 68 unique BAC clones and spans the whole H37Rv chromosome with the exception of a single gap of ~ 150 kb. As a postgenomic application, the canonical BAC set was used in a comparative study to reveal chromosomal polymorphisms between M. tuberculosis, M. bovis and M. bovis BCG Pasteur, and a novel 12.7 kb segment present in M. tuberculosis but absent from M. bovis and M. bovis BCG was characterized. This region contains a set of genes whose products show low similarity to proteins involved in polysaccharide biosynthesis. The H37Rv BAC library therefore provides the one skilled in the art with a powerful tool both for the generation and confirmation of sequence data as well as for comparative genomics and a plurality of postgenomic applications.

The above described BAC-based *Mycobacterium tuberculosis* genomic DNA library is part of the present invention and has been deposited in the Collection Nationale de Cultures de Microorganismes (CNCM) on November 19, 1997 under the accession number I-1945.

Another BAC-based DNA library has been constructed with the genomic DNA of *Mycobacterium bovis* BCG, Pasteur strain, and said DNA library has

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been deposited in the Collection Nationale de Cultures de Microorganismes (CNCM) on June 30, 1998 under the accession number I-2049.

Thus, as a specific embodiment of the above described method for isolating a polynucleotide of interest said method makes use of at least one BAC-based DNA library that has been constructed from the genomic DNA of *Mycobacterium tuberculosis*, more specifically of the H37Rv strain and particularly of the DNA library deposited in the accession number I-1945.

In another specific embodiment of the above described method for isolating a polynucleotide of interest said method makes use of at least one BAC-based DNA library has been constructed from the genomic DNA of *Mycobacterium bovis* BCG, more specifically of the Pasteur strain and particularly of the DNA library deposited in the accession number I-2049.

In more details, the method according to the invention for isolating a polynucleotide of interest may comprise the following steps:

- a) isolating at least one polynucleotide contained in a clone of a BAC-based DNA library of mycobacterial origin;
- b) isolating:
- at least one genomic or cDNA polynucleotide from a mycobacterium, said mycobacterium belonging to a strain different from the strain used to construct the BAC-based DNA library of step a); or alternatively
- at least one polynucleotide contained in a clone of a BAC-based DNA library prepared from the genome of a mycobacterium that is different from the mycobacterium used to construct the BAC-based DNA library of step a);
- c) hybridizing the at least one polynucleotide of step a) to the at least one polynucleotide of step b);
- d) selecting the at least one polynucleotide of step a) that has not formed a hybrid complex with the at least one polynucleotide of step b);
- e) characterizing the selected polynucleotide.

Following the above procedure, the at least one polynucleotide of step a) may be prepared as follows:

- 1) digesting at least one recombinant BAC clone by an appropriate resctriction endonuclease in order to isolate the polynucleotide insert of interest from the vector genetic material;
- 2) optionally amplifying the resulting polynucleotide insert;

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3) optionally digesting the polynucleotide insert of step 1) or step 2) with at least one restriction endonuclease.

The above method of the invention allows the one skilled in the art to perform comparative genomics between different strains or species of mycobacteria cells, for example between pathogenic strains or species and their non pathogenic strains or species counterparts, as it is the illustrative case for the genomic comparison between *Mycobacterium tuberculosis* and *Mycobacterium bovis* BCG that is described herein in the examples.

Restriction digests of a given clone of a BAC library according to the invention may be blotted to membranes, and then probed with radiolabeled DNA form another strain or another species of mycobacteria, allowing the one skilled in the art to identify, characterize and isolate a polynucleotide of interest that may be involved in important metabolical and/or physiological pathways of the mycobacterium under testing, such as a polynucleotide functionally involved in the pathogenicity of said given mycobacteria for its host organism.

More specifically, the inventors have shown in Example 6 that when restriction digests of a given clone of the BAC library identified by the CNCM accession number I-1945 are blotted to membranes and then probed with radiolabeled total genomic DNA from, for example, *Mycobacterium bovis* BCG Pasteur, it is observed that restriction fragments that fail to hybridize with the *M. bovis* BCG Pasteur DNA are absent from its genome, hence identifying polymorphic regions between *M. bovis* BCG Pasteur and *M. tuberculosis* H37Rv.

Thus, a further object of the present invention consists in a polynucleotide of interest that has been isolated according to the method described herein before.

In Example 6, a polynucleotide of approximately 12.7 kilobases has been isolated that is present in the genome of *M. tuberculosis* but is absent of the genome of *M. bovis* BCG. This polynucleotide of interest contains 11 ORFs that may be involved in polysaccharide biosynthesis. In particular, two of said ORFs are of particular interest, namely ORF6 (MTCY277.33; Rv1511) that encodes a protein that shares significant homology with bacterial GDP-D-mannose dehydratases, whereas the protein encoded by ORF7 (MTCY277.34; Rv1512) shares significant homology with a nucleotide sugar epimerase. As polysaccharide is a major constituent of the mycobacterial cell wall, these deleted genes may cause the cell wall of *M. bovis* BCG to differ from that of *M. tuberculosis*, a fact that may have important consequences for both the immune

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response to *M. bovis* BCG and virulence. Detection of such a polysaccharide is of diagnostic interest and possibly useful in the design of tuberculosis vaccines.

Consequently, the polynucleotide of interest obtained following the method according to the invention may contain at least one ORF, said ORF preferably encoding all or part of a polypeptide involved in an important metabolical and/or physiological pathway of the mycobacteria under testing, and more specifically all or part of a polypeptide that is involved in the pathogenicity of the mycobacteria under testing, such as for example *Mycobacterium tuberculosis*, and more generally mycobacteria belonging to the *Mycobacterium tuberculosis* complex.

The Mycobacterium tuberculosis complex has its usual meaning, i.e. the complex of mycobacteria causing tuberculosis which are Mycobacterium tuberculosis, Mycobacterium bovis, Mycobacterium africanum, Mycobacterium microti and the vaccine strain Mycobacterium bovis BCG.

An illustrative polynucleotide of interest according to the present invention comprises all or part of the polynucleotide of approximately 12.7 kilobases that is present in the genome of *M. tuberculosis* but is absent from the genome of *M. bovis* BCG disclosed hereinbefore. This polynucleotide is contained in clone Rv58 of the BAC DNA library I-1945.

Generally, the invention also pertains to a purified polynucleotide comprising the DNA insert contained in a recombinant BAC vector belonging to a BAC-based mycobacterial genomic DNA library, such as for example the I-1945 BAC DNA library.

Advantageously, such a polynucleotide has been identified according to the method of the invention.

Such a polynucleotide of interest may be used as a probe or a primer useful for specifically detecting a given mycobacterium of interest, such as *Mycobacterium tuberculosis* or *Mycobacterium bovis* BCG.

More specifically, the invention then deals with a purified polynucleotide useful as probe or a primer comprising all or part of the nucleotide sequence SEQ ID N°1.

The location, on the *Mycobacterium tuberculosis* chromosome, of the above polynucleotide of sequence SEQ ID N°1 has now been ascribed to begin, at its 5'end at nucleotide at position nt 1696015 and to end, at its 3'end, at nucleotide at position nt 1708746.

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For diagnostic purposes, this 12.7 kb deletion should allow a rapid PCR screening of tubercle isolates to identify whether they are bovine or human strains. The primers listed in Table 1 are flanking the deleted region and give a 722 bp amplicon in M. bovis or M. bovis BCG strains, but a fragment of 13,453 bp in M. tuberculosis that is practically impossible to amplify under the same PCR conditions. More importantly, assuming that some of the gene products from this region represent proteins with antigenic properties, it could be possible to develop a test that can reliably distinguish between the immune response induced by vaccination with M. bovis BCG vaccine strains and infection with M. tuberculosis or that the products (e.g. polysaccharides) are specific immunogens.

The invention also provides for a purified polynucleotide useful as a probe or as a primer, said polynucleotide being chosen in the following group of polynucleotides:

- a) a polynucleotide comprising at least 8 consecutive nucleotides of the sequence SEQ ID N°1;
- b) a polynucleotide whose sequence is fully complementary to the sequence of the polynucleotide defined in a);
- c) a polynucleotide that hybridizes under stringent hybridization conditions with the polynucleotide defined in a) or with the polynucleotide defined in b).

For the purpose of defining a polynucleotide or oligonucleotide hybridizing under stringent hybridization conditions, such as above, it is intended a polynucleotide that hybridizes with a reference polynucleotide under the following hybridization conditions.

The hybridization step is realized at 65°C in the presence of 6 x SSC buffer, 5 x Denhardt's solution, 0,5% SDS and 100µg/ml of salmon sperm DNA.

For technical information, 1 x SSC corresponds to 0.15 M NaCl and 0.05M sodium citrate; 1 x Denhardt's solution corresponds to 0.02% Ficoll, 0.02% polyvinylpyrrolidone and 0.02% bovine serum albumin.

The hybridization step is followed by four washing steps:

- two washings during 5 min, preferably at 65°C in a 2 x SSC and 0.1%SDS buffer,
  - one washing during 30 min, preferably at 65°C in a 2 x SSC and 0.1% SDS buffer,
- one washing during 10 min, preferably at 65°C in a 0.1 x SSC and 0.1%SDS buffer.

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A first illustrative useful polynucleotide that is included in the polynucleotide of sequence SEQ ID  $N^{\circ}1$  is the polynucleotide of sequence SEQ ID  $N^{\circ}2$  that corresponds to the Sp6 end-sequence of SEQ ID  $N^{\circ}1$ .

A second illustrative useful polynucleotide that is included in the polynucleotide of sequence SEQ ID N°1 is the polynucleotide of sequence SEQ ID N°3 that corresponds to the T7 end-sequence of SEQ ID N°1, located on the opposite strand.

The polynucleotide of sequence SEQ ID N°1 contains 11 ORFs, the respective locations of which, taking into account the orientation of each ORF on the chromosome, on the sequence of the *Mycobacterium tunerculosis* chromosome, is given hereafter:

- The location of ORF1 is comprised between nucleotide at position nt 1695944 and nucleotide at position nt1696441.
- The location of ORF2 is comprised between nucleotide at position nt 1696728 and nucleotide at position nt1697420.
  - The location of ORF3 is comprised between nucleotide at position nt 1698096 and nucleotide at position nt1699892. ORF3 probably encodes a protein having the characteristics of a membrane protein.
- The location of ORF4 is comprised between nucleotide at position nt 1700210 and nucleotide at position nt1701088.
- The location of ORF5 is comprised between nucleotide at position nt 1701293 and nucleotide at position nt1702588. ORF5 encodes a protein having the characteristics of a membrane protein.
- The location of ORF6 is comprised between nucleotide at position nt 1703072 and nucleotide at position nt1704091. ORF6 encodes a protein having the characteristics of a GDP-D-mannose dehydratase.
  - The location of ORF7 is comprised between nucleotide at position nt 1704091 and nucleotide at position nt1705056. ORF7 encodes a protein having the characteristics of a nucleotide sugar epimerase involved in colanic acid biosynthesis.
  - The location of ORF8 is comprised between nucleotide at position nt 1705056 and nucleotide at position nt1705784.
  - The location of ORF9 is comprised between nucleotide at position nt 1705808 and nucleotide at position nt1706593. ORF9 encodes a protein having the characteristics of colanic acid biosynthesis glycosyl transferase.

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- The location of ORF10 is comprised between nucleotide at position nt 1706631 and nucleotide at position nt1707524.

- The location of ORF11 is comprised between nucleotide at position nt 1707530 and nucleotide at position nt1708648. ORF11 encodes a protein similar to a spore coat polysaccharide biosynthesis.

A polynucleotide of interest obtained by the above-disclosed method according to the invention may also contain at least one ORF that encodes all or part of acidic, glycine-rich proteins, belonging to the PE and PPE families, whose genes are often clustered and based on multiple copies of the polymorphic repetitive sequences. The names PE and PPE derive from the fact that the motifs ProGlu (PE, positions 8, 9) and ProProGlu (PPE, positions 7 to 9) are found near the N-terminus in almost all cases. The PE protein family all have a highly conserved N-terminal domain of ~110 amino acid residues, that is predicted to have a globular structure, followed by a C-terminal segment which varies in size, sequence and repeat copy number. Phylogenetic analysis separated the PE family into several groups, the larger of which is the highly repetitive PGRS class containing 55 members whereas the other groups share very limited sequence similarity in their C-terminal domains. The predicted molecular weights of the PE proteins vary considerably as a few members only contain the ~110 amino acid N-terminal domain while the majority have C-terminal extensions ranging in size from 100 up to >1400 residues. A striking feature of the PGRS proteins is their exceptional glycine content (up to 50%) due to the presence of multiple tandem repetitions of GlyGlyAla or GlyGlyAsn motifs or variations thereof.

Like the PE family, the PPE protein family also has a conserved N-terminal domain that comprises ~180 amino acid residues followed by C-terminal segments that vary considerably in sequence and length. These proteins fall into at least three groups, one of which constitutes the MPTR class characterised by the presence of multiple, tandem copies of the motif AsnXGlyXGlyAsnXGly. The second subgroup contains a characteristic, well-conserved motif around position 350 (GlyXXSerValProXXTrp), whereas the other group contains proteins that are unrelated except for the presence of the common 180-residue PPE domain. C-terminal extensions may range in size from 00 up to 3500 residues.

One member of the PGRS sub-family, the WHO antigen 22T (Abou-Zeid et al., 1991), a 55kD protein capable of binding fibronectin, is produced during

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disease and elicits a variable antibody response suggesting either that individuals mount different immune responses or that this PGRS-protein may not be produced in this form by all strains of *M. tuberculosis*. In other words, at least some PE\_PGRS coding sequences encode for proteins that are involved in the recognition of *M. tuberculosis* by the immune system of the infected host. Therefore, differences in the PGRS sequences could represent the principal source of antigenic variation in the otherwise genetically and antigenically homogeneous bacterium.

By performing the method of the invention using the *M. tuberculosis* BAC based DNA library I-1945, the inventors have discovered the occurence of sequence differences between a given PGRS encoding ORF (ORF reference on the genomic sequence of *M. tuberculosis* Rv0746) of *M. tuberculosis* and its counterpart sequence in the genome of *M. bovis* BCG.

More precisely, the inventors have determined that one ORF contained in BAC vector N° Rv418 of the *M. tuberculosis* BCG I-1945 DNA library carries both base additions and base deletions when compared with the corresponding ORF in the genome of *M. bovis* BCG that is contained in the BAC vector N° X0175 of the *M. bovis* BCG I-2049 DNA libary. The variations observed in the base sequences correspond to variations in the C-terminal part of the aminoacid sequence of the PGRS ORF translation product.

As shown in Figure 6, an amino acid stretch of 9 residues in length is present in this *M. tuberculosis* PGRS (ORf reference Rv0746) and is absent from the ORF counterpart of *M. bovis* BCG, namely the following amino acid sequence:

25 NH2-GGAGGAGGSSAGGGGAGGAGGAGGWLLGD-COOH.

Furthermore, Figure 6 shows also that an amino acid stretch of 45 residues in length is absent from this *M. tuberculosis* PGRS and is present in the ORF counterpart of *M. bovis* BCG, namely following amino acid sequence:

NH2-GAGGIGGIGGNANGGAGGNGGTGGQLWGSGGAGVEGGAAL

SVGDT-COOH.

Similar observations were made with PPE ORF Rv0442, which showed a 5 codon deletion relative to a M. bovis amino acid sequence.

Given that the polymorphism associated with the PE-PGRS or PEE ORFS resulted in extensive antigeric variability or reduced antigen presentation, this would be of immense significance for vaccine design, for understanding

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protective immunity in tuberculosis and, possibly, explain the varied responses seen in different BCG vaccination programmes.

There are several striking parallels between the PGRS proteins and the Epstein-Barr virus-encoded nuclear antigens (EBNA). Both polypeptide families are glycine-rich, contain Gly-Ala repeats that represent more than one third of the molecule, and display variation in the length of the repeat region between different isolates. The Gly-Ala repeat region of EBNA1 has been shown to function as a cis-acting inhibitor of antigen processing and MHC class I-restricted antigen presentation (Levitskaya et al., 1995). The fact that MHC class I knock-out mice are extremely suscepible to M. tuberculosis underlines the importance of MHC class I antigen presentation in protection against tuberculosis. Therefore, it is possible that the PE/PPE protein family also play some role in inhibiting antigen presentation, allowing the bacillus to hide from the host's immune system.

As such the novel and nonobvious PGRS polynucleotide from *M. bovis* which is homolog to the *M. tuberculosis* ORF Rv0746, and which is contained in the BAC clone N° X0175 (See Table 4 for SP6 and T7 end-sequences of clone n° X0175) of the I-2049 *M. bovis* BCG BAC DNA library is part of the present invention, as it represents a starting material in order to define specific probes or primers useful for detection of antigenic variability in mycobacterial strains, possible inhibition of antigen processing as well as to differentiate *M. tuberculosis* from *M. bovis* BCG.

Thus, a further object of the invention consists in a polynucleotide comprising the sequence SEQ ID N°4.

Polynucleotides of interest have been defined by the inventors as useful detection tools in order to differentiate *M. tuberculosis* from *M. bovis* BCG. Such polynucleotides are contained in the 45 aminoacid length coding sequence that is present in *M. bovis* BCG but absent from *M. tuberculosis*. This polynucleotide has a sequence beginning (5'end) at the nucleotide at position nt 729 of the sequence SEQ ID N°4 and ending (3'end) at the nucleotide in position nt 863 of the sequence SEQ ID N°4.

Thus, part of the present invention is also a polynucleotide which is chosen among the following group of polynucleotides:

a) a polynucleotide comprising at least 8 consecutive nucleotides of the nucleotide sequence SEQ ID  $N^{\circ}5$ ;

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b) a polynucleotide which sequence is fully complementary to the sequence of the polynucleotide defined in a);

c) a polynucleotide that hybridizes under stringent hybridization conditions with the polynucleotide defined in a) or with the polynucleotide defined in b).

The stringent hybridization conditions for the purpose of defining the above disclosed polynucleotide are defined herein before in the specification.

The invention also provides for a BAC-based *Mycobacterium tuberculosis* strain H37Rv genomic DNA library that has been deposited in the Collection Nationale de Cultures de Microorganismes on November 19, 1997 under the accession number I-1945.

A further object of the invention consists in a recombinant BAC vector which is chosen among the group consisting of the recombinant BAC vectors belonging to the BAC-based DNA library I-1945.

Generally, a recombinant BAC vector of interest may be chosen among the following set or group of BAC vectors contained in the BAC-based DNA library I-1945:

library I-1945:
Rv101; Rv102; Rv103; Rv104; Rv105; Rv106; Rv107; Rv108; Rv109; Rv10;
Rv110; Rv111; Rv112; Rv113; Rv114; Rv115; Rv116; Rv117; Rv118; Rv119;
Rv11; Rv120; Rv121; Rv122; Rv123; Rv124; Rv126; Rv127; Rv128; Rv129;
Rv130; Rv132; Rv134; Rv135; Rv136; Rv137; Rv138; Rv139; Rv13; Rv140;
Rv141; Rv142; Rv143; Rv144; Rv145; Rv146; Rv147; Rv148; Rv149; Rv14;
Rv150; Rv151; Rv152; Rv153; Rv154; Rv155; Rv156; Rv157; Rv159; Rv15;
Rv160; Rv161; Rv162; Rv163; Rv164; Rv165; Rv166; Rv167; Rv169; Rv16;
Rv170; Rv171; Rv172; Rv173; Rv174; Rv175; Rv176; Rv177; Rv178; Rv179;
Rv17; Rv180; Rv181; Rv182; Rv183; Rv184; Rv185; Rv186; Rv187; Rv188;
Rv18; Rv190; Rv191; Rv192; Rv193; Rv194; Rv195; Rv196; Rv19; Rv1; Rv201;
Rv204; Rv205; Rv207; Rv209; Rv20; Rv214; Rv215; Rv217; Rv218; Rv219;
Rv21; Rv220; Rv221; Rv222; Rv223; Rv224; Rv225; Rv226; Rv227; Rv228;
Rv229; Rv22; Rv230; Rv231; Rv232; Rv234; Rv235; Rv237; Rv240;
Rv241; Rv243; Rv244; Rv245; Rv246; Rv247; Rv249; Rv24; Rv251; Rv252;

Rv241; Rv243; Rv244; Rv245; Rv246; Rv247; Rv249; Rv24; Rv251; Rv252; Rv253; Rv254; Rv255; Rv257; Rv258; Rv259; Rv25; Rv260; Rv261; Rv262; Rv263; Rv264; Rv265; Rv266; Rv267; Rv268; Rv269; Rv26; Rv270; Rv271; Rv272; Rv273; Rv274; Rv275; Rv276; Rv277; Rv278; Rv279; Rv27; Rv280; Rv281; Rv282; Rv283; Rv284; Rv285; Rv286; Rv287; Rv288; Rv289; Rv28;

35 Rv290; Rv291; Rv292; Rv293; Rv294; Rv295; Rv296; Rv29; Rv2, Rv301;

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Rv302; Rv303; Rv304; Rv306; Rv307; Rv308; Rv309; Rv30; Rv310; Rv311; Rv312: Rv313: Rv314; Rv315; Rv316; Rv317; Rv318; Rv319; Rv31; Rv32; Rv322; Rv327; Rv328; Rv329; Rv32; Rv330; Rv331; Rv333; Rv334; Rv335; Rv336; Rv337; Rv338; Rv339; Rv33; Rv340; Rv341; Rv343; Rv344; Rv346; Rv347; Rv348; Rv349; Rv34; Rv350; Rv351; Rv352; Rv353; Rv354; Rv355; 5 Rv356: Rv357: Rv358: Rv359: Rv35; Rv360: Rv361: Rv363; Rv364; Rv365; Rv366; Rv367; Rv368; Rv369; Rv36; Rv370; Rv371; Rv373; Rv374; Rv375; Rv376; Rv377; Rv378; Rv379; Rv37; Rv381; Rv382; Rv383; Rv384; Rv385; Rv386; Rv387; Rv388; Rv389; Rv38; Rv390; Rv391; Rv392; Rv393; Rv396; Rv39; Rv3; Rv40; Rv412; Rv413; Rv414; Rv415; Rv416; Rv417; Rv418; Rv419; 10 Rv41; Rv42; Rv43; Rv44; Rv45; Rv46; Rv47; Rv48; Rv49; Rv4; Rv50; Rv51; Rv52; Rv53; Rv54; Rv55; Rv56; Rv57; Rv58; Rv59; Rv5; Rv60; Rv61; Rv62; Rv63; Rv64; Rv65; Rv66; Rv67; Rv68; Rv69; Rv6; Rv70; Rv71; Rv72; Rv73; Rv74; Rv75; Rv76; Rv77; Rv78; Rv79; Rv7; Rv80; Rv81; Rv82; Rv83; Rv84; Rv85; Rv86; Rv87; Rv88; Rv89; Rv8; Rv90; Rv91; Rv92; Rv94; Rv95; Rv96; 15 Rv9.

The end sequences of the polynucleotide inserts of each of the above clones corresponding respectively to the sequences adjacent to the T7 promoter and to the Sp6 promoter on the BAC vector are shown in Table 3.

It has been shown by the inventors that the minimal overlapping set of BAC vectors of the BAC-based DNA library I-1945 contains 68 unique BAC clones and practically spans almost the whole H37Rv chromosome with the exception of a single gap of approximately 150 kb.

More specifically, a recombinant BAC vector of interest is choosen among the following set or group of BAC vectors from the BAC-based DNA library I-1945, the location of which vector DNA inserts on the chromosome of M. tuberculosis is shown in Figure 3:

Rv234; Rv351; Rv166; Rv35; Rv415; Rv404; Rv209; Rv272; Rv30; Rv228; Rv233; Rb38; Rv280; Rv177; Rv48; Rv374; Rv151; Rv238; Rv156; Rv92; Rv3; Rv403; Rv322; Rv243; Rv330; Rv285; Rv233; Rv219; Rv416; Rv67; Rv222; Rv149; Rv279; Rv87; Rv273; Rv266; Rv25; Rv136; Rv414; Rv13; Rv289; Rv60; Rv104; Rv5; Rv165; Rv215; Rv329; Rv240; Rv19; Rv74; Rv411; Rv167; Rv56; Rv80; Rv164; Rv59; Rv313; Rv265; Rv308; Rv220; Rv258; Rv339; Rv121; Rv419; Rv418; Rv45; Rv217; Rv134; Rv17; Rv103; Rv21; Rv22; Rv270; Rv267; Rv174; Rv257; Rv44; Rv71; Rv7; Rv27; Rv191; Rv230; Rv128; Rv407;

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Rv106; Rv39; Rv255; Rv74; Rv355; Rv268; Rv58; Rv173; Rv264; Rv417; Rv401; Rv144; Rv302; Rv81; Rv163; Rv281; Rv221; Rv420; Rv175; Rv86; Rv412; Rv73; Rv269; Rv214; Rv287; Rv42; Rv143.

The polynucleotides disclosed in Table 3 may be used as probes in order to select a given clone of the BAC DNA library I-1945 for further use.

The invention also provides for a BAC-based *Mycobacterium bovis* strain Pasteur genomic DNA library that has been deposited in the Collection Nationale de Cultures de Microorganismes on June 30, 1998 under the accession number I-2049.

A further object of the invention consists in a recombinant BAC vector which is chosen among the group consisting of the recombinant BAC vectors belonging to the BAC-based DNA library I-2049. This DNA library contains approximately 1600 clones. The average insert size is estimated to be ~80 kb.

Generally, a recombinant BAC vector of interest may be chosen among the following set or group of BAC vectors contained in the BAC-based DNA library I-2049:

X0001; X0002; X0003; X0004; X0006; X0007; X0008; X0009; X0010; X0012; X0013; X0014; X0015; X0016; X0017; X0018; X0019; X0020; X0021; X0175.

The end sequences of the polynucleotide inserts of each of the above clones corresponding respectively to the sequences adjacent to the T7 promoter and to the Sp6 promoter on the BAC vector are shown in Table 4.

The polynucleotides disclosed in Table 4 may be used as probes in order to select a given clone of the BAC DNA library I-2049 for further use.

Are also part of the invention the polynucleotide inserts that are contained in the above described BAC vectors, that are useful as primers or probes.

These polynucleotides and nucleic acid fragments may be used as primers for use in amplification reactions, or as nucleic probes.

PCR is described in the US patent N° 4,683,202. The amplified fragments may be identified by an agarose or a polyacrylamide gel electrophoresis, or by a capillary electrophoresis or alternatively by a chromatography technique (gel filtration, hydrophobic chromatography or ion exchange chromatography). The specificity of the amplification may be ensured by a molecular hybridization using, for example, one of the initial primers as nucleic probes.

Amplified nucleotide fragments are used as probes in hybridization reactions in order to detect the presence of one polynucleotide according to the

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present invention or in order to detect mutations in the genome of the given mycobacterium of interest, specifically a mycobacterium belonging to the *Mycobacterium tuberculosis* complex and more specifically *Mycobacterium tuberculosis* and *Mycobacterium bovis* BCG.

Are also part of the present invention the amplified nucleic fragments (« amplicons ») defined herein above.

These probes and amplicons may be radioactively or non-radioactively labeled, using for example enzymes or fluorescent compounds.

Other techniques related to nucleic acid amplification may also be used and are generally preferred to the PCR technique.

The Strand Displacement Amplification (SDA) technique (Walker et al., 1992) is an isothermal amplification technique based on the ability of a restriction enzyme to cleave one of the strands at his recognition site (which is under a hemiphosphorothioate form) and on the property of a DNA polymerase to initiate the synthesis of a new strand from the 3'OH end generated by the restriction enzyme and on the property of this DNA polymerase to displace the previously synthesized strand being localized downstream. The SDA method comprises two main steps:

- a) The synthesis, in the presence of dCTP-alpha-S, of DNA molecules that are flanked by the restriction sites that may be cleaved by an appropriate enzyme.
- b) The exponential amplification of these DNA molecules modified as such, by ezyme cleavage, strand displacement and copying of the displaced strands. The steps of cleavage, strand displacement and copy are repeated a sufficient number of times in order to obtain an accurate sensitivity of the assay.

The SDA technique was initially realized using the restriction endonuclease HincII but is now generally practised with an endonuclease from *Bacillus stearothermophilus* (BSOBI) and a fragment of a DNA polymerase which is devoid of any 5'→3'exonuclease activity isolated from *Bacillus cladotenax* (exo- Bca) [=exo-minus-Bca]. Both enzymes are able to operate at 60°C and the system is now optimized in order to allow the use of dUTP and the decontamination by UDG. When unsing this technique, as described by Spargo et al. in 1996, the doubling time of the target DNA is of 26 seconds and the amplification rate is of 10<sup>10</sup> after an incubation time of 15 min at 60°C.

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The SDA amplification technique is more easy to perform than PCR (a single thermostated waterbath device is necessary) and is faster thant the other amplification methods.

Thus, another object of the present invention consists in using the nucleic acid fragments according to the invention (primers) in a method of DNA or RNA amplification according to the SDA technique. For performing SDA, two pairs of primers are used: a pair of external primers (B1, B2) consisting of a sequence specific for the target polynucleotide of interest and a pair of internal primers (S1, S2) consisting of a fusion oligonucleotide carrying a site that is recognized by a restriction endonuclease, for exemple the enzyme BSOBI.

The operating conditions to perform SDA with such primers are described in Spargo et al, 1996.

The polynucleotides of the invention and their above described fragments, especially the primers according to the invention, are useful as technical means for performing different target nucleic acid amplification methods such as:

- TAS (Transcription-based Amplification System), described by Kwoh et al. in 1989.
- SR (Self-Sustained Sequence Replication), described by Guatelli et al.in 1990.
- NASBA (Nucleic acid Sequence Based Amplification), described by Kievitis et al. in 1991.
- TMA (Transcription Mediated Amplification).

The polynucleotides according to the invention are also useful as technical means for performing methods for amplification or modification of a nucleic acid used as a probe, such as:

- 25 LCR (Ligase Chain Reaction), described by Landegren et al. in 1988 and improved by Barany et al. in 1991 who employ a thermostable ligase.
  - RCR (Repair Chain Reaction) described by Segev et al. in 1992.
  - CPR (Cycling Probe Reaction), described by Duck et al. in 1990.
- Q-beta replicase reaction, described by Miele et al. in 1983 and improved by
  Chu et al. in 1986, Lizardi et al. in 1988 and by Burg et al. and Stone et al. in 1996.

When the target polynucleotide to be detected is a RNA, for example a mRNA, a reverse transcriptase enzyme will be used before the amplification reaction in order to obtain a cDNA from the RNA contained in the biological sample. The generated cDNA is subsequently used as the nucleic acid target for

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the primers or the probes used in an amplification process or a detection process according to the present invention.

The non-labeled polynucleotides or oligonucleotides of the invention may be directly used as probes. Nevertheless, the polynucleotides or oligonucleotides are generally labeled with a radioactive element (<sup>32</sup>P, <sup>35</sup>S, <sup>3</sup>H, <sup>125</sup>I) or by a non-isotopic molecule (for example, biotin, acetylaminofluorene, digoxigenin, 5-bromodesoxyuridin, fluorescein) in order to generate probes that are useful for numerous applications.

Examples of non-radioactive labeling of nucleic acid fragments are described in the french patent N° FR-7810975 or by Urdea et al. or Sanchez-Pescador et al., 1988.

In the latter case, other labeling techniques may be also used such as those described in the french patents FR-2 422 956 and 2 518 755. The hybridization step may be performed in different ways (Matthews et al., 1988). The more general method consists of immobilizing the nucleic acid that has been extracted from the biological sample onto a substrate (nitrocellulose, nylon, polystyrene) and then to incubate, in defined conditions, the target nucleic acid with the probe. Subsequently to the hybridization step, the excess amount of the specific probe is discarded and the hybrid molecules formed are detected by an appropriate method (radioactivity, fluorescence or enzyme activity measurement).

Advantageously, the probes according to the present invention may have structural characteristics such that they allow the signal amplification, such structural characteristics being, for example, branched DNA probes as those described by Urdea et al. in 1991 or in the European patent N° EP-0 225 807 (Chiron).

In another advantageous embodiment of the probes according to the present invention, the latters may be used as « capture probes », and are for this purpose immobilized on a substrate in order to capture the target nucleic acid contained in a biological sample. The captured target nucleic acid is subsequently detected with a second probe which recognizes a sequence of the target nucleic acid which is different from the sequence recognized by the capture probe.

The oligonucleotide probes according to the present invention may also be used in a detection device comprising a matrix library of probes immobilized on a substrate, the sequence of each probe of a given length being localized in a shift of one or several bases, one from the other, each probe of the matrix library thus

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being complementary to a distinct sequence of the target nucleic acid. Optionally, the substrate of the matrix may be a material able to act as an electron donor, the detection of the matrix poisitons in which an hybridization has occurred being subsequently determined by an electronic device. Such matrix libraries of probes and methods of specific detection of a targer nucleic acid is described in the European patent application N° EP-0 713 016 (Affymax technologies) and also in the US patent N° US-5,202,231 (Drmanac).

Since almost the whole length of a mycobacterial chromososme is covered by a BAC-based genomic DNA libraries according to the present invention (i.e. 97% of the *M. tuberculosis* chromosome is covered by the BAC library I-1945), these DNA libraries will play an important role in a plurality of post-genomic applications, such as in mycobacterial gene expression studies where the canonical set of BACs could be used as a matrix for hybridization studies. Probing such matrices with cDNA probes prepared from total mRNA will uncover genetic loci induced or repressed under different physiological conditions (Chuang et al., 1993; Trieselmann et al., 1992). As such, the H37Rv BAC library represents a fundamental resource for present and future genomics investigations.

The BAC vectors or the polynucleotide inserts contained therein may be directly used as probes, for example when immobilized on a substrate such as described herein before.

The BAC vectors or their polynucleotide inserts may be directly asdorbed on a nitrocellulose membrane, at predetermined locations on which one or several polynucleotides to be tested are then put to hybridize therewith.

Preferably, a collection of BAC vectors that spans the whole genome of the mycobacterium under testing will be immobilized, such as, for example, the set of 68 BAC vectors of the I-1945 DNA library that is described elsewhere in the specification and shown in Figure 3.

The immobilization and hybridization steps may be performed as described in the present Materials and Methods Section.

As another illustrative embodiment of the use of the BAC vectors of the invention as polynucleotide probes, these vectors may be useful to perform a transcriptional activity analysis of mycobacteria growing in different environmental conditions, for example under conditions in which a stress response is expected, as it is the case at an elevated temperature, for example 40°C.

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In this specific embodiment of the invention, Genescreen membranes may be used to immobilize the restriction endonuclease digests (*Hind*III digests for the BAC DNA library I-1945) of the BAC vectors by transfer from a gel (Trieselmann et al., 1992).

Alternatively, the BAC vectors may be immobilized for dot blot experiments as follows. First, the DNA concentration of each BAC clone is determined by hybridization of blots of clone DNAs and of a BAC vector concentration standard with a BAC vector specific DNA probe. Hybridization is quantified by the Betascope 603 blot analyzer (Betagen Corp.), which colects beta particles directly from the blot with high efficiency. Then, 0.5 µg of each clone DNA is incubated in 0.25 M NaOH and 10 mM EDTA at 65°C for 60 min to denature the DNA and degrade residual RNA contaminants. By using a manifold filtration system (21 by 21 wells), each clone DNA is blotted onto a GeneScreen Plus nylon membrane in the alkaline solution. After neutralization, the blots are baked at 85°C for 2 h under vacuum. Positive and negative controls are added when necessary. In order to perform this procedure, it may be referred to the article of Chuang et al. (1993).

For RNA extractions, cells grown in a suitable volume of culture medium may, for example, be immediately mixed with an equal volume of crushed ice at  $70^{\circ}$ C and spun at  $4^{\circ}$ C in a 50 ml centrifugation tube. The cell pellet is then suspended in 0.6 ml of ice-cold buffer (10 mM KCl, 5 mM MgCl, 10 mM Tris; pH 7.4) and then immediately added to 0.6 ml of hot lysis buffer (0.4 M NaCl, 40 mM EDTA, 1% beta-mercaptoethanol, 1% SDS, 20 mM Tris; pH 7.4) containing 100  $\mu$ l of water saturated phenol. This mixture is incubated in a boiling water bath for 40 s. The debris are removed by centrifugation. The supernatant is extracted with phenol-chloroform five times, ethanol precipitated, and dried. The dried RNA pellet is dissolved in water before use.

Then labeled total cDNA may be prepared by the following method. The reaction mixture contains 15  $\mu g$  of the previously prepared total RNA, 5  $\mu g$  of pd(N<sub>6</sub>) (random hexamers from Pharmacia Inc.), 0.5 mM dATP, 0.5 mM dGTP and 0.5mM DTTP, 5 $\mu$ M dCTP, 100  $\mu$ Ci of [ $\alpha$ -<sup>32</sup>P]dCTP (3,000 Ci/mmol), 50 mM Tris-HCl (pH 8.3), 6 mM MgCl<sub>2</sub>, 40 mM Kcl, 0.5 U of avian myeloblastosis virus reverse transcriptase (Life Science Inc.) in a total volume of 50  $\mu$ l. The reaction is allowed to continue overnight at room temperature. EDTA and NaOH are then added to final concentrations of 50 mM and 0.25 M, respectively, and

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the mixture is incubated at 65°C for 30 min to degrade the RNA templates. The cDNA is then ready to use after neutralization by adding Hcl and Tris buffer.

The hybridization step may be performed as described by Chuang et al. (1993) and briefly disclosed hereinafter. The DNA dot blot is hybridized to <sup>32</sup>P-labeled total cDNA in a solution containing 0.1% polyvinylpyrrolidone, 0.1% Ficoll, 0.1% sodium Ppi, 0.1% bovine serum albumin, 0.5% SDS, 100 mM NaCl, and 0.1 mM sodium citrate, pH 7.2, at 65°C for 2 days and then washed with a solution containing 0.1% SDS, 100 mM NaCl, and 10 mM Na-citrate, pH 7.2. The same dot blot is used for hybridization with both control and experimental cDNAs, with an alkaline probe stripping procedure (soaked twice in 0.25M NaOH-0.75 M NaCl at room temperature, 30 min each, neutralized, and completely dried at 65°C for at least 30 min) between the two hybridizations. Quantification may be done with the Betascope 603 blot analyzer (Betagen Corp.).

As it flows from the above technical teachings, another object of the invention consists in a method for detecting the presence of mycobateria in a biological sample comprising the steps of:

- a) bringing into contact the recombinant BAC vector or a purified polynucleotide according to the invention with a biological sample;
- b) detecting the hybrid nucleic acid molecule formed between said purified polynucleotide and the nucleic acid molecules contained within the biological sample.

The invention further deals with a method for detecting the presence of mycobacteria in a biological sample comprising the steps of:

- a) bringing into contact the recombinant BAC vector or a purified polynucleotide according to the invention that has been immobilized onto a substrate with a biological sample;
  - b) bringing into contact the hybrid nucleic acid molecule formed between said purified polynucleotide and the nucleic acid contained in the biological sample with a labeled recombinant BAC vector or a polynucleotide according to the invention, provided that said polynucleotide and polynucleotide of step a) have non-overlapping sequences.

Another object of the invention consists in a method for detecting the presence of mycobacteria in a biological sample comprising the steps of:

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- a) bringing into contact the nucleic acid molecules contained in the biological sample with a pair of primers according to the invention;
- b) amplifying said nucleic acid molecules;
- c) detecting the nucleic acid fragments that have been amplified, for example by gel electrophoresis or with a labeled polynucleotide according to the invention.

In one specific embodiment of the above detection and/or amplification methods, said methods comprise an additional step wherein before step a), the nucleic acid molecules of the biological sample have been made available to a hybridization reaction.

In another specific embodiment of the above detection methods, said methods comprise an additional step, wherein, before the detection step, the nucleic acid molecules that are not hybridized with the immobilized purified polynucleotide are removed.

Also part of the invention is a kit for detecting mycobacteria in a biological sample comprising:

- a) a recombinant BAC vector or a purified polynucleotide according to the invention;
- b) reagents necessary to perform a nucleic acid hybridization reaction.

The invention also pertains to a kit for detecting a mycobacteria in a biological sample comprising:

- a) a recombinant BAC vector or a purified polynucleotide according to the invention that is immobilized onto a substrate:
- b) reagents necessary to perform a nucleic acid hybridization reaction;
- c) a purified polynucleotide according to the invention which is radioactively or non-radioactively labeled, provided that said polynucleotide and the polynucleotide of step a) have non-overlapping sequences.

Moreover, the invention provides for a kit for detecting mycobacteria in a biological sample comprising:

- a) a pair of purified primers according to the invention;
- b) reagents necessary to perform a nucleic acid amplification reaction;
  - c) optionally, a purified polynucleotide according to the invention useful as a probe.

The invention embraces also a method for detecting the presence of a genomic DNA, a cDNA or a mRNA of mycobacteria in a biological sample, comprising the steps of:

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a) bringing into contact the biological sample with a plurality of BAC vectors according to the invention or purified polynucleotides according to the invention, that are immobilized on a substrate;

b) detecting the hybrid complexes formed.

The invention also provides a kit for detecting the presence of genomic DNA, cDNA or mRNA of a mycobacterium in a biological sample, comprising:

- a) a substrate on which a plurality of BAC vectors according to the invention or purified polynucleotides according to the invention have been immobilized;
- b) optionally, the reagents necessary to perform the hybridization reaction.

Additionally, the recombinant BAC vectors according to the invention and the polynucleotide inserts contained therein may be used for performing detection methods based on « molecular combing ». Said methods consist in methods for aligning macromolecules, especially DNA and are applied to processes for detecting, for measuring intramolecular distance, for separating and/or for assaying a macromolecule, especially DNA in a sample.

These « molecular combing » methods are simple methods, where the triple line S/A/B (meniscus) resulting form the contact between a solvent A and the surface S and a medium B is caused to move on the said surface S, the said macromolecules (i.e. DNA) having a part, especially an end, anchored on the surface S, the other part, especially the other end, being in solution in the solvent A. These methods are particularly fully described in the PCT Application n° PCT/FR 95/00165 files on February 11, 1994 (Bensimon et al.).

When performing the « molecular combing » method with the recombinant BAC vectors according to the inventions or their polynucleotide inserts, the latters may be immobilized (« anchored ») on a suitable substrate and aligned as described in the PCT Application n° PCT/FR 95/00165, the whole teachings of this PCT Application being herien incorporated by reference. Then, polynucleotides to be tested, preferably under the form of radioactively or non radioactively labeled polynucleotides, that may consist of fragments of genomic DNA, cDNA etc. are brought into contact with the previously aligned polynucleotides according to the present invention and then their hybridization position on the aligned DNA molecules is determined using any suitable means including a microscope or a suitable camera device.

Thus, the present invention is also directed to a method for the detection of the presence of a polynucleotide of mycobacterial origin in a biological sample

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and/or for physical mapping of a polynucleotide on a genomic DNA, said method comprising :

- a) aligning at least one polynucleotide contained in a recombinant BAC vector according to the invention on the surface of a substrate;
- b) bringing into contact at least one polynucleotide to be tested with the substrate on which the at least one polynucleotide of step a) has been aligned;
  - c) detecting the presence and/or the location of the tested polynucleotide on the at least one aligned polynucleotide of step a).

The invention finally provides for a kit for performing the above method, comprising:

- a) a substrate whose surface has at least one polynucleotide contained in a recombinant BAC vector according to the invention;
- b) optionally, reagents necessary for labeling DNA;
- c) optionnally, reagents necessary for performing a hybridization reaction.

In conclusion, it may be underlined that the alliance of such BAC-based approaches such as described in the present specification to the advances in comparative genomics by the availability of an increased number of complete genomes, and the rapid increase of well-characterized gene products in the public databases, will allow the one skilled in the art an exhaustive analysis of the mycobacterial genome.

#### MATERIALS AND METHODS

- 1. DNA-preparation. Preparation of *M. tuberculosis* H37Rv DNA in agarose plugs was conducted as previously described (Canard et al., 1989; Philipp et al., 1996b). Plugs were stored in 0.2 M EDTA at 48C at 1 at 1.2 in a - 25 1996b). Plugs were stored in 0.2 M EDTA at 4°C and washed 3 times in 0.1% Triton X-100 buffer prior to use.
  - 2. BAC vector preparation. pBeloBAC11 was kindly provided by Dr. Shizuya, Department of Biology, California Institute of Technology (Pasadena, CA). The preparation followed the description of Woo et al., 1994 (Woo et al., 1994).
- 30 3. Partial digestion with *HindIII*. Partial digestion was carried out on plugs, each containing approximately 10 μg of high molecular weight DNA, after three one hour equilibration steps in 50 ml of *HindIII* 1X digestion buffer (Boehringer Mannheim, Mannheim, Germany) plus 0.1% Triton X-100. The buffer was then removed and replaced by 1ml/plug of ice-cold *HindIII* enzyme buffer containing
- 35 20 units of HindIII (Boehringer). After two hours incubation on ice, the plugs

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were transferred to a 37°C water bath for 30 minutes. Digestions were stopped by adding 500 µl of 50 mM EDTA (pH 8.0).

- 4. Size selection. The partially digested DNA was subjected to contour-clamped homogenous electric field (CHEF) electrophoresis on a 1% agarose gel using a BioRad DR III apparatus (BioRad, Hercules, CA) in 1X TAE buffer at 13°C, with a ramp from 3 to 15 seconds at 6 V/cm for 16 hours. Agarose slices from 25 to 75 kb, 75 to 120 kb and 120 to 180 kb were excised from the gel and stored in TE at 4°C.
- 5. Ligation and transformation. Agarose-slices containing fractions from 25 to 75 kb, 75 to 120 kb and 120 to 180 kb were melted at 65°C for 10 minutes and digested with Gelase (Epicentre Technologies, Madison, WI), using 1 unit per 100 µl gel-slice. 25-100 ng of the size-selected DNA was then ligated to 10 ng of HindIII digested, dephosphorylated pBeloBAC11 in a 1:10 molar ratio using 10 units of T4 DNA ligase (New England Biolabs, Beverly, MA) at 16°C for 20 hours. Ligation mixtures were heated at 65°C for 15 minutes, then drop-dialysed against TE using Millipore VS 0.025 mM membranes (Millipore, Bedford, MA). Fresh electrocompetent E. coli DH10B cells (Sheng et al., 1995) were harvested from 200 ml of a mid-log (OD550=0.5) culture grown in SOB medium. Cells were washed three times in ice-cold water, and finally resuspended in ice-cold water to a cell density of  $10^{11}$  cells/ml (OD550=150). 1  $\mu$ l of the ligation-mix was used for electroporation of 30 µl of electrocompetent DH10B E. coli using a Eurogentec Easyject Plus electroporator (Eurogentec, Seraing, Belgium), with settings of 2.5 kV, 25  $\mu F$ , and 99  $\Omega$ , in 2 mm wide electroporation cuvettes. After electroporation, cells were resuspended in 600 µl of SOC medium, allowed to recover for 45 minutes at 37°C with gentle shaking, and then plated on LB agar containing 12.5  $\mu$ g/ml chloramphenicol (CM), 50  $\mu$ g/ml X-gal, and 25  $\mu$ g/ml IPTG. The plates were incubated overnight and recombinants (white colonies) were picked manually to 96 well plates. Each clone was inoculated 3 times (2 X 200  $\mu l$  and 1 X 100  $\mu l$  of 2YT/12.5  $\mu g/ml$  CM per clone) and incubated overnight. One of the microtiter plates, containing 100 µl culture per well, was maintained as a master plate at - 80°C after 100 ml of 80% glycerol were added to each well, while minipreps (Sambrook et al., 1989) were prepared from the remaining two plates to check for the presence of inserts. Clones containing inserts were then designated "Rv" clones, repicked from the master plate to a second set of plates for storage of the library at -80°C.

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6. Preparation of DNA for sizing, direct sequencing and comparative genomics. A modified Birnboim and Doly protocol (Birnboim et al., 1979) was used for extraction of plasmid DNA for sequencing purposes. Each Rv clone was inoculated into a 50 ml Falcon polypropylene tube containing 40 ml of 2YT medium with 12.5 µg/ml of CM and grown overnight at 37°C with shaking. Cells were harvested by centrifugation and stored at -20°C. The frozen pellet was resuspended in 4 ml of Solution A (50 mM glucose, 10 mM EDTA, 25 mM Tris, pH 8.0) and 4 ml of freshly prepared solution B (0.2 M NaOH, 0.2% SDS) was then added. The solution was gently mixed and kept at room temperature for 5 minutes before adding 4 ml of ice-cold solution C (3M Sodium Acetate, pH 4.7). Tubes were kept on ice for 15 min, and centrifuged at 10,000 rpm for 15 min. After isopropanol precipitation, the DNA pellet was dissolved in 600 µl RNase solution (15 mM Tris HCl pH 8.0, 10 µg/ml RNase A). After 30 minutes at 37°C the DNA solution was extracted with chloroform:isoamylalcohol (24:1) and precipitated from the aqueous phase using isopropanol. The DNA pellet was then rinsed with 70% ethanol, air-dried and dissolved in 30 µl distilled water. In general, DNA prepared by this method was clean and concentrated enough to give good quality results by automatic sequencing (at least 300 bp of sequence). For a few DNA preparations, an additional polyethylene glycol (PEG) precipitation step was necessary, which was performed as follows. The 30 ul of DNA solution were diluted to 64µl, mixed gently and precipitated using 16 µl 4M NaCl and 80 µl of 13% PEG 8000. After 30 min on ice the tubes were centrifuged at 4°C, the pellet carefully rinsed with 70% ethanol, air-dried and diluted in 20 µl of distilled water.

7. Sizing of inserts. Insert sizes were determined by pulsed-field gel electrophoresis (PFGE) after cleavage with *DraI* (Promega). 100-200 ng of DNA was *DraI*-cleaved in 20 μl total reaction volume, following the manufacturer's recommendations, then loaded onto a 1% agarose gel and migrated using a pulse of 4 s for 15 h at 6.25 V/cm at 10°C on an LKB-Pharmacia CHEF apparatus.

Mid-range and low-range PFGE markers (New England Biolabs) were used as size standards. Insert sizes were estimated after ethidium bromide staining of gels.

8. Direct sequencing. For each sequencing reaction 7 μl BAC DNA (300-500ng), 2 μl primer (2 μM), 8 μl reaction mix of the *Taq* DyeDeoxy Terminator cycle sequencing kit (Applied Biosystems) and 3 μl distilled water were used.

After 26 cycles (96°C for 30 sec; 56°C for 15 sec; 60°C for 4 min) in a thermocycler (MJ-research Inc., Watertown, MA) DNA was precipitated using 70 µl of 70% ethanol/0.5 mM MgCl<sub>2</sub>, centrifuged, rinsed with 70% ethanol, dried and dissolved in 2 µl of formamide/EDTA buffer. SP6 and T7 samples of 32 BAC clones were loaded onto 64 lane, 6% polyacrylamide gels and electrophoresis was performed on a Model 373A automatic DNA sequencer (Applied Biosystems) for 12 to 16 hours. The sequences of oligonucleotides used as primers are shown in Table 1.

- 9. DOP-PCR. As an alternate procedure we used partially degenerate oligonucleotides in combination with vector-specific (SP6 or T7) primers to amplify insert ends of BAC clones, following a previously published protocol for P1 clones (Liu et al., 1995). The degenerate primers Deg2, Deg3, Deg4, Deg6 (Table 1) gave the best results for selected amplification of insert termini.
- 15 Table 1: Primers used for PCRs and sequencing

Vector specific Primers for DOP PCR- first amplification step:

SP6-BAC1: AGT TAG CTC ACT CAT TAG GCA

T7-BAC1: GGA TGT GCT GCA AGG CGA TTA

Vector specific Primers (direct sequencing, nested primer for second PCR step)

20 SP6 Mid: AAA CAG CTA TGA CCA TGA TTA CGC CAA

T7-Belo2: TCC TCT AGA GTC GAC CTG CAG GCA

**Degenerate Primers:** 

Deg2: TCT AGA NNN NNN TCC GGC

Deg3: TCT AGA NNN NNN GGG CCC

25 Deg4: CGT TTA AAN NNN NWA GGC CG

Deg6: GGT ACT AGT NNN NNW TCC GGC

Primers used for the amplification of *M. bovis* DNA in polymorphic chromosomal region of Rv58:

Primer 1: ACG ACC TCA TAT TCC GAA TCC C

- 30 Primer 2: GCA TCT GTT GAG TAC GCA CTT CC
  - 10. Screening by pooled PCR. To identify particular clones in the library which could not be detected by random end-sequencing of the 400 BAC clones, PCR-screening of DNA pools was performed. Primers were designed for regions of the chromosome where no BAC coverage was expected with a particular training account.
- 35 chromosome where no BAC coverage was appearent using cosmid-or H37Rv

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whole genome shotgun sequences. Primers were designed to amplify approximately 400-500 bp. Ninety-six-well plates containing 200 2YT/12.5 µg/ml CM per well were inoculated with 5 µl of -80°C glycerol stock cultures each from the master plates and incubated overnight. The 96 clones of each plate were pooled by taking 20 µl of culture from each well and this procedure was repeated for 31 plates. Pooled cultures were centrifuged, the pellets were resuspended in sterile water, boiled for 5 minutes, centrifuged and the supernatants kept for PCRs. As an initial screening step, the 31 pools of a total of 2976 BACs, representing about two thirds of the library were tested for the presence of a specific clone using appropriate PCR primers. PCR was performed using 10 µl of supernatant, 5 µl of assay buffer (100 mM bmercaptoethanol, 600 mM Tris HCl (pH 8.8), 20 mM MgCl<sub>2</sub>, 170 mM (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>), 5 μl of Dimethylsulfoxide (DMSO), 5 μl of dNTPs (20 mM), 5 μl of water, 10 µl primer (2 µM), 10 µl inverse primer (2 µM) and 0.2 units of Tag DNA polymerase (Boehringer). 32 cycles of PCR (95°C for 30 s, 55°C for 1 min 30 s, 72°C for 2 min) were performed after an initial denaturation at 95°C for 1 min. An extension step at 72 °C for 5 min finished the PCR. If a pool of 96 clones yielded an appropriate PCR product (Fig. 1A), subpools were made to identify the specific clone. Subpools representative for lane A of a 96 well plate were made by pooling clones 1 to 12 from lane A into a separate tube. Subpools for lanes B to H were made in the same way. In addition, subpools of each of the 12 rows (containing 8 clones each) were made, so that for one 96 well plate, 20 subpools were obtained. PCR with these 20 subpools identified the specific clone (Fig. 1B, lower gel portion). If more than one specific clone was present among the 96 clones of one plate (Fig. 1B, upper gel portion), additional PCR reactions had to be performed with the possible candidates (data not shown).

11. Genomic comparisons. DNA from the BAC clone Rv58 was digested with the restriction endonucleases *Eco*RI and *Pvu*II, and resolved by agarose gel electrophoresis at low voltage overnight (1.5 V/cm). DNA was transferred via the method of Southern to nitrocellulose membranes (Hybond C extra, Amersham) following standard protocols (Sambrook et al., 1989), then fixed to the membranes at 80°C for 2 hours. The blot was hybridized with <sup>32</sup>P labelled total genomic DNA from *M. tuberculosis* H37Rv, *M. bovis* type strain (ATCC 19210) or *M. bovis* BCG Pasteur. Hybridization was performed at 37°C overnight in

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50% formamide hybridization buffer as previously described (Philipp et al., 1996b). Results were interpreted from the autoradiograms.

12. Computer analysis. Sequence data from the automated sequencer ABI373A were transferred as binary data to a Digital Alpha 200 station or Sun SparcII station and analysed using TED, a sequence analysis program from the Staden software package (Dear et al., 1991). Proof-read sequences were compared using the BLAST programs (Altschul et al., 1990) to the *M. tuberculosis* H37Rv sequence databases of the Sanger Centre, containing the collected cosmid sequences (TB.dbs) and whole-genome shotgun reads (TB\_shotgun\_all.dbs) (http://www.sanger.ac.uk/). In addition, local databases containing 1520 cosmid end-sequences and the accumulating BAC end-sequences were used to determine the exact location of end-sequenced BACs on the physical and genetic map. MycDB (Bergh et al., 1994) and public databases (EMBL, Genbank) were also used to compare new sequences, but to a lesser extent. The organization of the open reading frames (ORFs) in the polymorphic region of clone Rv58 was determined using the DIANA software established at the Sanger Centre.

## **EXAMPLES**

Example 1: Construction of a pBeloBAC11 library of *M. tuberculosis* H37Rv.

Partial HindIII fragments of H37Rv DNA in the size range of 25 to 180 kb were ligated into pBeloBAC11 and electroporated into strain E. coli DH10B. While cloning of fractions I (25 to 75 kb) and II (75 to 120 kb) gave approximately 4 x 10<sup>4</sup> transformants (white colonies), cloning of fraction III (120 to 180 kb) repeatedly resulted in empty clones. Parallel cloning experiments using partial HindIII digests of human DNA resulted in stable inserts for all three fractions (data not shown), suggesting that the maximum size of large inserts in BAC clones is strongly dependent on the source of the DNA. Analysis of the clones for the presence of inserts revealed that 70 % of the clones had an insert of the appropriate size while the remaining 30% of white colonies represented empty or lacZ'-mutated clones. Size determination of randomly selected, Dral-cleaved BACs via PFGE showed that the insert sizes ranged for the majority of the clones between 40 kb and 100 kb with an average size of 70 kb. Clones with inserts of appropriate size were designated with "Rv" numbers, recultured and stored at -80°C for further use.

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## Example 2: Direct DNA sequence analysis of BACs.

To characterize the BAC clones, they were systematically subjected to insert termini sequencing. Two approaches, direct sequencing of BAC DNA and PCR with degenerate oligonucleotide primers (DOP), adapted to the high G+C content of mycobacterial DNA, were used. In a first screening phase, 50 BAC clones designated Rv1 to Rv50 were analysed using both methods in parallel. Except for two clones, where the sequences diverged significantly, the sequences obtained by the two methods only differed in length. Sequences obtained directly were on average about 350 bp long and for 95% of the clones both the SP6 and T7 end-sequences were obtained at the first attempt. Sequences obtained by DOP-PCR were mostly shorter than 300 bp. For 40% of the BACs we obtained only very short amplicons of 50 to 100 base pairs from one end. In two cases the sequence obtained with the DOP-PCR differed from the sequences obtained by direct sequencing, and in these cases E.coli or vector sequences were amplified (data not shown). Taking the advantages and disadvantages of both methods into account, we decided to use direct termini sequencing for the systematic determination of the SP6 and T7 end-sequences.

### Example 3: Representativity of the library.

After having determined the end-sequences of 400 BACs a certain redundancy was seen. The majority of clones were represented at least 3 to 4 times. Maximum redundancy was seen in the vicinity of the unique rrn operon, as 2.5 % of the clones carried identical fragments that bridge the cosmids Y50 and Y130 (Fig. 3, approximate position at 1440 kb). The majority of clones with identical inserts appeared as two variants, corresponding to both possible orientations of the HindIII fragment in pBeloBAC11. This suggests that the redundancy was not the result of amplification during library construction, but due to the limited number of possible combinations of partial HindIII fragments in the given size-range of 25 to 120 kb. To detect rare BAC clones, a pooled PCR protocol was used. Primers were designed on the basis of the existing cosmid sequences and used to screen 31 pools of 96 BAC clones. When positive PCR products of the correct size were obtained, smaller subpools (of 8 or 12 clones each) of the corresponding pool were subsequently used to identify the corresponding clone (Figs. 1A and 1B). With this approach 20 additional BACs (Rv401-Rv420) were found for the regions where no BACs were found with the initial systematic sequencing approach. The end-sequences of these BACs

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(Rv401-420) were determined by direct sequencing, which confirmed the predicted location of the clones on the chromosome. A 97% coverage of the genome of H37Rv with BAC clones was obtained. Only one region of  $\sim$  150 kb was apparently not represented in the BAC library as screening of all pools with several sets of specific primers did not reveal the corresponding clone. This was probably due to the fact that *Hin*dIII fragments of mycobacterial DNA larger than 110 kb are very difficult to establish in *E. coli* and that a *Hin*dIII fragment of  $\sim$ 120 kb is present in this region of the chromosome (data not shown).

## Example 4: Establishing a BAC map.

Using all end-sequence and shotgun-sequence data from the H37Rv genome sequencing project, most of the BAC clones could then be localized by sequence comparison on the integrated map of the chromosome of M. tuberculosis strain H37Rv (Philipp et al., 1996b) and an ordered physical map of the BAC-clones was established. PCR with primers from the termini sequences of selected BACs were used for chromosomal walking and confirmation of overlapping BACs (data not shown). The correct order of BACs on the map was also confirmed more recently, using 40,000 whole genome shotgun reads established at the Sanger Centre. In addition, pulsed-field gel electrophoresis of DraI digests of selected BACs was performed (Fig. 2) in order to see if the approximate fragment size and the presence or absence of Dral cleavage sites in the insert were consistent with the location of the BACs on the physical map (Fig. 3). Comparison of the sequence-based BAC-map with the physical and genetic map, established by PFGE and hybridization experiments (Philipp et al., 1996b), showed that the two maps were in good agreement. The positions of 8 genetic markers previously shown on the physical and genetic map were directly confirmed by BAC-end-sequence data (Table 2, Fig. 3). The position of 43 from 47 Y-clones (91%) shown on the physical and genetic map, which were later shotgun sequenced, was confirmed by the BAC end-sequences and shotgun sequence data. Four clones (Y63, Y180, Y251, and Y253) were located to different positions than previously thought and this was found to be due to book keeping errors or to chimeric inserts. Their present approximate location relative to the oriC is shown in Figure 3: Y63 at 380 kb, Y63A at 2300 kb, Y180 at 2160 kb, Y251 at 100 kb, and Y253 at 2700 kb. A total of 48 BACs, covering regions of the chromosome, not represented by cosmids were then shotgun sequenced (Cole et al., 1997), and these are squared in Fig. 3. No chimeric BACs

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were found, which is consistent with the observations of other research groups for other BAC libraries (Cai et al., 1995; Zimmer et al., 1997). The absence of chimeric BACs was of particular importance for the correct assembly of the *M. tuberculosis* H37Rv sequence. The exact position of the BAC termini sequences on the chromosome will be available via the world wide web (http://www.pasteur.fr/MycDB).

Table 2: Identities of genetic markers previously shown on the integrated and genetic map of H37Rv (Phlipp et al., 1996b) wich showed perfect sequence homology with BAC ens sequences.

Locus	BAC end	Description of genetic marker	Organism	GenBank Accession
F'' ' ' ' ' ' ' ' ' ' ' ' ' ' ' ' ' ' '	sequence			n°
ара	Rv163SP6	Secreted		
		alanine-proline-rich antigen	M. tuberculosis	X80268
dnaJ, dnaK	Rv164T7	DnaJ hsp	M. leprae	M95576
fop-A	Rv136T7	Fibronectin binding protein	M. tuberculosis	M27016
polA	Rv401T7	DNA polymerase I	M. tuberculosis	L11920
ponA	Rv273T7	Penicillin binding protein	M. leprae	S82044
pstC	Rv103T7	Putative	M. tuberculosis	Z48057
		phosphate transport receptor		
recA	Rv415SP6	Homologous recombination	M. tuberculosis	X58485
wag9	Rv35SP6	35-kDa antigen	M. tuberculosis	M69187

# Example 5: Repetitive end-sequences.

Repetitive sequences can seriously confound mapping and sequence assembly. In the case of the BAC end-sequences, no particular problems with repetitive sequences were observed. Although nine clones with one end in an IS1081 (Collins et al., 1991) sequence were identified, it was possible to correctly locate their position on the map using the sequence of the second terminus. Moreover, these BACs were used to determine the exact locations of IS1081 sequences on the map. Five copies of this insertion sequence, which

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harbors a *Hind*III cleavage site, were mapped on the previous physical and genetic map. In contrast, BAC end-sequence data revealed an additional copy of IS1081 on the *M. tuberculosis* H37Rv chromosome. The additional copy was identified by six clones (Rv27, Rv118, Rv142, Rv160, Rv190, Rv371) which harbored an identical fragment linking Y50 to I364 (Fig. 3, at ~ 1380 kb). This copy of IS1081 was not found by previous hybridization experiments probably because it is located near another copy of IS1081, localized on the same *DraI* fragment Z7 and *AsnI* fragment U (Fig. 3, at ~ 1140 kb). Furthermore, the position of a copy of IS1081 previously shown in *DraI* fragment Y1 (Fig. 3, at ~ 1840 kb) had to be changed to the region of Y349 (Fig. 3, at ~ 3340 kb) according to the end-sequences of BAC Rv223. The positions of the four other IS1081 copies were confirmed by the sequence data and therefore remained unchanged. In total 6 copies of IS1081 were identified in the H37Rv genome in agreement with the findings of others (Collins et al., 1991).

In addition, a sequence of 1165 bp in length containing a *Hin*dIII site was found in two copies in the genome of H37Rv in different regions. The end-sequences of BAC clones Rv48 and Rv374, covering cosmid Y164, as well as Rv419 and Rv45, that cover cosmid Y92, had perfect identity with the corresponding parts of this 1165 bp sequence (Fig. 3, at ~ 3480 kb and ~ 900 kb). Analysis of the sequence did not reveal any homology with insertion sequences or other repetitive elements. However, as each of the two locations showed appropriate BAC coverage, chimerism of the sequenced cosmids Y164 and Y92 can be ruled out as the probable cause.

# Example 6: Using BAC clones in comparative genomics.

The minimal overlapping set of BAC clones represents a powerful tool for comparative genomics. For example, with each BAC clone containing on average an insert of 70 kb, it should be possible to cover a 1Mb section of the chromosome with 15 BAC clones. Restriction digests of overlapping clones can then be blotted to membranes, and probed with radiolabelled total genomic DNA from, for example, *M. bovis* BCG Pasteur. Restriction fragments that fail to hybridize with the *M. bovis* BCG Pasteur DNA must be absent from its genome, hence identifying polymorphic regions between *M. bovis* BCG Pasteur and *M. tuberculosis* H37Rv. The results of such an analysis with clone Rv58 (Fig. 3, at ~1680 kb) are shown here. This clone covers a previously described polymorphic genomic region between *M. tuberculosis* and *M. bovis* BCG strains (Philipp et

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al., 1996a). EcoRI and PvuII digests from clone Rv58, fixed on nitrocellulose membranes, were hybridized with  $^{32}P$ -labelled total genomic DNA from M. tuberculosis H37Rv, M. bovis (ATCC 19120), and M. bovis BCG Pasteur. Figures 4A and 4B present the results of this analysis, where it is clear that several restriction fragments from clone Rv58 failed to hybridize with genomic DNA from either M. bovis or M. bovis BCG Pasteur. On the basis of the various missing restriction fragments, a restriction map of the polymorphic region was established and compared to the H37Rv sequence data. The localization of the polymorphism could therefore be estimated, and appropriate oligonucleotide primers (Table 1) were selected for the amplification and sequencing of the corresponding region in M. bovis. The alignment of M. bovis and M. tuberculosis H37Rv sequences showed that 12,732 bp were absent from the chromosomal region of the M. bovis type strain and M. bovis BCG Pasteur strain. The G+C content of the polymorphic region is 62.3 mol%, which is the same as the average genome G+C content of the M. tuberculosis genome, hence indicating that this region is not a prophage or other such insertion. Subsequent PCR studies revealed that this segment was also absent from the Danish, Russian, and Glaxo substrains of M. bovis BCG, suggesting that this polymorphism can be used to distinguish M. bovis from M. tuberculosis. Analysis of this sequence showed that 11 putative open reading frames (ORFs) are present in M. tuberculosis, corresponding to ORFs MTCY277.28 to MTCY277.38 / accession number Z79701 -EMBL Nucleotide Sequence Data Library (Fig. 5). FASTA searches against the protein and nucleic acid databases revealed that the genes of this region may be involved in polysaccharide biosynthesis. Among these putative genes, the highest score was seen with ORF 6 (MTCY277.33), whose putative product shows a 51.9% identity with GDP-D-Mannose dehydratase from Pseudomonas aeruginosa (accession number U18320 - EMBL Nucleotide Sequence Data Library) in a 320 amino acid overlap. The novel M. bovis sequence of the polymorphic region was deposited under accession number AJ003103 in the EMBL Nucleotide Sequence Data Library.

As it appears from the teachings of the specification, the invention is not limited in scope to one or several of the above detailed embodiments; the present invention also embraces all the alternatives that can be performed by one skilled in the same technical field, without deviating from the subject or from the scope of the instant invention.

**Table 3:** End-sequences of the polynucleotide inserts cloned in the named recombinant BAC vectors contained in the I-1945 *M. tuberculosis* H37Rv genomic DNA library.

RvXXXSP6 corresponds to the SP6 end-sequence of the clone RvXXX.

RvXXXT7 corresponds to the T7 end-sequence of the clone RvXXX.

RvXXXIS 1081 corresponds to a region located close to a copy of the IS1081 repetitive sequence (Insertion element).

The character « - » denotes an uncertain base residue.

### Clone Rv101

AATACTCAAGCTTGCCCAGCCGTCGATGACAAGAATATGTCCGCAAAAGACTCAGCGGCCGACTTTGCTCGCAGCTG
GCGGTACCGCGCCACCGATTCTATGCCGTGGTCGCGGAAAAATGCCTCCCGAAATCGCACGGCCGACTCCAGTTCGGC
GAGCATCCGCGATGCCAGCTGCGGCCCTGCCGGCCACGGCACCCACATGCGGCAGTTCGTCCACCTGGGCCAG
CGCCCCGCCGCCGAATTCCAAACAATAGAACTGCACCCGGCCCGCATCGTGGGTAACAGCCAACGCCATGATCAGCGT
CCGCAGCGCGGTTGACTTGCCGTTTGCGGTGCACCTACGAACGCCACTTGCCTGCGGCCCCGGACAAGTCGATCGT
GCGCGCACCCGTGACTGCTCTAACGGGCGATTGAAATTCCGAT

# Clone Rv102

AATACTCAAGCTTTCCGCCGATACCCGCCATGTCGCGCACATCCAGGACTTCTGGGGGGGATCCGCTGACAGCGGCGGGATCCCAAAGTGCGGATGATCGGGCCGCCTACGTCGTGGTGTACCTCGTCGTAACAACGAAACCGAAGCGTATGACTCGGTCCACGCGGTGCGGCACATGGTGGACACCACCGCCACCGCACGGGGTGAAGGCCTATGTCACCGGTCCGGCAGCACCACCGCCACCGCGACCGCGATCACCAACATGGTGATCGCCAGCAAAAAGTATCGCTAAGGTCACCGCGATCACCAACATGGTGATCGCCAGCAACATGGTGATCGCCAGCAACATGGTGATCGCCAGCAACATGGTGATCGCCAGCAACATGGTGATCGCCAGCAACATGGTGATCGCCAGCAACATGGTGATCACCAGCGGTTCT

### Clone Rv103

AATACTCAAGCTTTCGGCGGAAACGGACACATTGCGAATATTGATGACAAAATAAAATCATTGATGGTTTGAGTCACCAGGCCGATCAAGCCTTCGCCGAGCCAAATTCCAATCAAGAGGCCCAAGCCCGTACCAATCAGCCCGAACGACGGGATCCGTCATTATCAGCCCAAAATAACTGCTCTCGGGTTACACCCCAAACAGCGCAATATGGCGAAAAAACGGTCGCCGTTGCACGACATTAAATGTCACGGTATTGTAGATTAAAAAGATACCCAC

TGCTCCCGAAACCTGGGGGTGTGCCTGCTCTGTATGCACGGCATACGGACATCCTTCCCCTGAGACCCGCGGTCGAACCAGCCACGTGTCCATCATAGNGGGTCAACCCCGGCCAAGGGCGACGGCACGCCAAGTTCGCCGACCGTTAACCTAGTGCTGTTAGCTTCATTTGCTGCGGATCAAAACAGCTGGTCGGCCGTTAGGAACTGAATTGAAACTCAACCGATTTGGTGCCGCCGTAGGTGTCCTCGGCTGCGGGTGCGCTGTGTTTTCCCGCGTGTGGTAACGACGACAATGTGACCGGGGGAGGTGCAACCACTGGCCAGGCGTCGGCAAAGGTCGATTGCGGGGGGGAAGAAGACACTCAAAGCCAGTGGGT

Clone Rv104

TCCTATGTCCCTGCCGAGCANGTGATCGAACGCGGTGACAGATTTGTCTATCCTGGACCTGACGGTGAGGTCGAAGTT
TTCCAGGAATTCGGCAAAATCGGTAAGAGCCTGAAGAATTCGGTATCGCCGGACGAAATCTGCGACGCATACGGGGGC
ATATACGCTTCGGGTTTACGAGATGTCGATGGGGCCGCTGGAGGCTTCACGTCCATGGGCCACAAAGGATGTTGTCGG
CGCGTACCGTTTTCTGCAGCGGGTGTGGCGCTTGGTCG

Clone Rv105

GGTACGCTTCGGTCGCAGTCTGCGAGTGATGCATGACGACCGGGACCTCGTCGGCATCTTCCATAGCCCGCCACACCT
TCAGTTGCTCACCGGAATCCAACCGGTAGAAGGTCGGCGAGCGCTCGGCATTGGTCATCGGGATATGCCGCTCGGGAC
GGTCAGAGCCCTCGGGTCCGGCCAGCACTCCGCAGGCTTCGTCGGGGTGGTCGCGACGCCATGGGCCACCATCGCAT
TCACCAGGTCTGCGCGAATCACCAGCACGTAGACGGTTCCTTTCCTAAGCAACACCGAAGTTTCAGGACCCGAATGCT
CCGGGAAACATGTCACGGTAGGTCGGTATTCCGGCTACCGGCTGA

Clone Rv106

GGCTNGCGTACCGGCTGCGCGGGCCTACCACGTGCCGGAACTGGAAGCGCAGTAAGCCCTCAACGCGCCACCG
CTTTGGCCCGCGCGCGCGCGTAGGCGCATCGGCGGTGGCCGTGGGGCGGCACTGCGACCTCACCAGCGGCTTTCG
AGCTTTGTTCGATCAACCGGCCAGCATGGTCGANGATGCATTCGAGACCATATTCGAAATTGGTTTCATCGGGGGCCC
CGATCCGATGCCCCCCCCAGTTGCGTGAGCAANCAGCGGAGTCNTCGCGGGATCGATGGCCACCGGGGTGTTCAATGG
CGGATGGTCCGCTGCCCGCCGACTGGCTCTTGCGGGAGAACCGATCTAGCACCACCGATCCGCGCACGTNG

Clone Rv107

CGTAATNTCGCGCACANCCANGACTTCTGGGGGGGATCNGCTGACAGTGGTNGGATCCCAAATTGCGGATGATCGGGCC
GCCNACGTCGTTGTGTACCTCNTCNGTCACAACNAANCCGAANCGTATGACTCGGTCCACGCGGTGCGGCACATGGTG
GACACCACCGCCACCGCNCGGGGTGAAGGCCTATGTCACCGGTCCGGCAACACTCAATGCCGACCAGGCCGANGCC
GGACACNANAGTATCNCTAACGTCACCGCGATCACGAGCATGGTGATCGNNCAATGTTNCTANTGATCTATCGCTCCG
TAATTACCGCGGTTCTCGTCTTGATCATGGTCGCANCGAACTCCGGCGCAATCCGCGGATTCATCGNCTTGCTCGCCG
ATCACATATTTTCAGCCTTTCACATTGCAACNAACCTGCTCGTCTCATGGNGATGCGGCGACACCGGACTACCGATATC
ATGCTCGCCGTTACACAATCNCGCCACGCCGCGAAGACNGGAAACGCTTCTACACAATNTTCNCGGGACGCCACTNAA
CTTGGTTCNGGTTTGACATTGCCGCGCATGTNTGCCCAGCTTTGCCGGCTCCCCTTA

Clone Rv108

Clone Rv109

GACCGNNCCATGTTTCCACAATGTGGTGCCAGTNCGGNGGCTACGTGCCATCNANACACTGGCGCAGGCTATCGCACC
CGTTATCNGCTACGAACAAATCNCGGTATGCGTTCTTTANCATGAGTCGGCGACCGNCGATCATGGTCGACACCCACG
ACNGAAATACGCAGATCGCCNTCNAGCNTGTGTGCCGCGGATTATCANGACTGACCTCCTGGCTGACCGGNNTGTNTG
GTCGCGATGCCTGGCGCCCGGCCGGCGTGNTCGTGGTCGGCTCGGATAGCGAAGTCAGCTAATTCTCGTGGCAGCTCG
AAAGGGTCCTGCCGGTGCCGGTCTTTGCGCAAACCATGCNCATGTTACGGTCCCTCGGGTGCGGCCTGGCGGCGGC

Clone Rv10

GGGATGGCCGGCCCCTAAACTCTTCGTGTTCCACTAACTCCGGGAGGGNCAATCTCGGGCCGTTATGGCTCACGTCGCGCCCCTCCGACCGCGAACATTCGGAGTTGGCAGCAACCTGGTAGCACCTTGGCCGG

NCCGTCGTTGACAAGTAAATATGTCCGCAAAAGTCTCAGCGGCCGACTTTGCTCGCAGGTGGCGGTACCGCCCCCGAGTCGATGCCGTGGTCGCGGAAGAATGCCTCCCGAAATCGCACGGCCTTCCCNNTTTAAACGGA

Clone Rv110

CTACACCATCGAATACGACGCGTCGCCNACTTTCCGCGGTACCCGCTCAACTTTGTGTCGACCCTCAACGCCATTGCCGCCACTCGACGCCTCAACGCCATTGCCGCCCCTACTACTTCCTCAACTCCTGACGCCGGAACAAATTGACGCAGCGGTTCCGCTGACCAATACGGTCGTCCCACGATGACCCACTGCATCATCATCATCCGCACGGANAACCTGCCGCTGCTAGAGCCACTGCGATCGGTGCCGATCGTGGGGAACCCACTGGCGAACCTGGTTCAACCAAACTTGAANGTGATTGTTAACCTGGGCTACNGCGACCCGGCCTATGGTTATTCNACCTCNCCGCCCAATGTTGCGACTCCGTTCGGGTTGTTCCCANAAGTCNNCCCGGTCGTCATCGCCGAANCTCTCCTCCCGGGACCCACAGGGAATCNGCNATTTCNCCTACAAATCANCCACCTCCA

Clone Rv111

GCATGATCGGCCACCTTTCGGGCCGCCCGGCATACGGCGGCGTACCGATCTCCGCGTCATACACCCGCGGGTAATCGCCGACGGTGCCGGTTCGCGAGCCGAAGGTGACGACTCTGATTGAATCGAGTTCCAGGTCCAGCGGGTGGCGCACCAACGGCGGAGCTCAACGACGTCAACGACCTCAACGACCTCAACGACCTCAACGACCTCAACGACCCTGGTGACCGTAGTTCNCCCG

Clone Rv112

GACACTATAGAATACTCAAGCTTGCCAACCGCCAGCCTGCATCCGGCGGCGANCACTGCTCCGCCGACCAGTACGAAC
CAACCTGCGGTGCCCAGGCCATTGACGATGTGCTGGTCGGCGCCCGCGAGTCCGCGCACCATCAACGCCGCGGGCACC
ACCANGGCGGCCCCACCCTGCACGGCGACGATCATTCCGGCGCCGCTCACGGCGGGGGGCTCGAACANGCACAGCA
TCAACGTNGTCACCCGGCCGTGACCGGCCCGCATCGTCACACCCCAAGCCCATTGCCGTCCTCCAACNGGGCGA
CCCGGCCCGCATCGTCACACGGNCTAAGGCCATTGCCGTCCTCCT

TCGGCGCCATCGGCACCTTCGAGGACCTGTATTTCGACGCCGTGGCCNACCTGAGGTTGGCGGTGGACNAAGTGTGCA CCCGGTTGATTCGCTCGGCCTTGCCGGATGCCACCCNGCGCCTGGTGGTCGATCCGCNAANAGACAANTTGTGGTGGA NGCTTCTGCTGCCTGCGACACCCACNACGTGGTGGCACCGGGCAGCTTTAGCTGGCATGTCCTGACCGCGCTGGCCGA CNACTCCAGACNTTCCACNAANGGTCGCCNNCCCAATGTNCCGNANTGTCTCCGGNTCCCTTTACCNCCCAATGGGCN GNTTCCACNGGTTACGGGCCCCNTNCCGGCGGGTCTNCCTCCCAANCTACCAAATACGCCCGACNTTCCGGA

### Clone Rv113

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### Clone Rv114

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CAAGCTATTTAGGTGACACTATAGAATACTCAAGCTTCGCGTCTACGCCGGCCCGGAGCATCCGCACAGCGCTCAGCA
GCCGGTTCCGTACGANCTCAAGCAGGTGGCGCAATGACCGAAACCACCCCAGCCCCGCAAACCCCGGCGCCCCGCC
GGGCCCGCACAATCGTTCGTGTTGGAGCGGCCCATCCANACCGTTGGGCGCCCGTAAGGANGCCGTGGTACGAATGCGG
CTGGTGCCCGGCACCGGCAAGTTCGACCTCAACGGCCGCAGCTTGGANGACTACTTCCCAAACAAGGTGCACCAGCAG
TTGATCAAGGCACCCTGGTCACCGTGGATCGGGTGGAAAGTTTCGACATCTTTGCCCACCTGGGCGGCGGCGCCGT
CCGGTCAGGCCGGGCCTGCCCTGGGTATCGCCCGGGCATTGATTCTGGTATCCCCNGAAGAACCG

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CGGTTGGCCACCGCTTCTGCGGTGCCGCCGCCGTCGACAATGACCGTGTCGTCCTTGCTGACCACCACCACGCGTCGGGCC
GAGCCCAGCACCTCCAAGCCCACCTCGCGCAGCACCATGCCGGCGTTGACCACCTTGACCACCTCACCACC
GCCAGGTCCTCAAGGAAACGCCTTACGGCGGTCACCGAAGTACGGCCCCTTGACCGCGACCGCTTTCAACGTCTTGCG
AATCGCGTTGACGACCAGCGTCGCCAACGCTTCGCCCTCCACGTCTTCAGCCACGATCAGTAGTGGCTTACCCGTTCC
TGCAACCTTTTCCAGCAATGGCAACAGATCGGGAAGCGAACTGATCTTGTCTTGGTGCN

### Clone Rv115

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CCAAGCTATTTAGGTGACACTATAGAATACTCAAGCTTTTGGCTGGGTCGCCTTCGAATTCNGCGTGCACCGCTATGG
GTTGCANCAGCGGCTGGCCGCACACCCCACTGGCCCGGGTGTTTTCGCCCCGAACCCGGATCATGGTGAGCGAAAA
GGANATTCNCCTGTTCGATGCTGGGATTCGCCACGCCAAGGCATCTANCGATTACTCTCCNCGGGGTGGGAAAAGTGC
CCAATCCCCCTCCCAACTTTCCNAACAATCATTCCGGTTCCNCCNTCCGGTTGGNGGTAACCNNCCAATAAAACC
CCTGCCCG

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### Clone Rv116

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CCACCCGTGTATTTTGGGATGGCAAAAAGGCGAAGCACCGCGTGGCCACGAACGCCGGGAGGACAATCTCGGGCGG CTAGGGCTTCTCGCGGGAAGGCCCGAACGTACGGCGTTTCAACACGTCGCCTCCGCCCTCCGACCGCGAACATTCGGGG ATGGCAGCAACCTGGTAGCACCCTGGCCGGCGATGATCTGCAGCGTCGCCGCGGGTAGTCGCCCCCGGGCGGCTAC AGTCTGAAACGCGATGACCATCGATGTGTGGATGCAGCATCCGACGCAACGGTTCCTACACGGCGATATGTTCGCCTC

### Clone Rv117

### Clone Rv118

GAGGCAGCTTCGCCGGCAATTCTÂCTAGCGAGAAGTCTGGCCCGATACGGATCTGACCGAAGTCGCTGCGGTGCAGCC
CACCCTCATTGGCGATGGCGCCGACGATGGCGCCTGGACCGATGTTGTGCCGCTTGCCGACGCGACGCGTAGGTGG
TCAAGTCCGGTCTACGCTTGGGCCTTTGCGGACGGTCCGACGCTGGTCGCGGTTGCGCCGCAAAGCGGCGGGTCGG
GTGCCATCAGGAATGCCTCACCGCCGCGGCACTGCACGCCAGTGCCGCGGATGTCAGCCATCGGGACATCATGCT
CGCGTTCATACTCCTCGACCAGTCGGCGAACAGCTCGATTCCCGGGACATCGCGCAATCGCGAATCGCCAACCCCCCGCGCCCAGCGCCTTTGCCGCGTAGCCTTTTC
ATC

## Clone Rv119

## Clone Rv11

### Clone Rv120

ATACTCAAGCTTCAGTTCCTCCACGACGCGTTCCCAAATGAATTTCCCGATCCCACAATCTCGGTTCAGATACAGGTCGCCATACCCCTTACTTCGGCAACGCTGGGCGGATTGGCCCTGCCGCTGCACCAAACCATCAACGCCTTCAAATTGCCGGCCAATCTCGTTCAGCCCAATCCAT

### Clone Rv121

ATACTCAAGCTTGCCAAAGAGACCTCGTCCACCAAGCAGGACGCGACCGTCGAGGTGGCGATCCGGCTTGGCGTCGACCCGCGTAAGGCAAACCAGATGGTTCGCGGCACGGCACCGCACCACCGGCACTGGTTAAGAACTGCCCGCGTCGCGCTTTTCGCGGTTGGTGAAAAAGGCCAATGCCTGCGTTTGCCGTGGGGGGCGGATGTTGTCGGGAGTGACAATCTGATCAAAAGGATTCAAGGCCGGTTGGCTGGAATTCAATGCCGCAATCGCGACACCGG

CCACGGCGTGGATCAAGGTACCGGCCGGGATGTTGCGCAATGGCAGGTTGTTGCCCGGCTTGATGTCGGCGTTAGCGCCGATTCCACCACATCCCCTTGCGAAAGTCCGTTGGGTGCAATGATGTAGCGCTTCTCCCCATCGAGATAGTGGAGCAACCCAATCCGTGCGGTACGGGTCGTACTCGATGTGCGCGACCTTGGCGTTGACACCATCTTTGTCATTGCGGCGAAAGTCGATCATCCGGTAAGCGCGCTTATGACCGCCGCCTTTGTGCCGGGTGGTAATCCGGCCATGCGCGTTGCGTCCACCGGGACGTGCAGCGGCGCACCAGCGACTTCTCCGGGGTTGACCGGGTNATCTC

### Clone Rv122

### Clone Ry

TGGGCGCCTCTTTCGGCCTTCCCNNTTTAAACGNAGCANGACATTCTGGGTATCGAGTTGTACTGGATGGTGTTGGCGATGTCGGCGATGGTGATCGGCGATGGTGAAACAGAGAAATTGGGATGGTGAACACCGGAATTATCCGTGCCATGGCTGGTACCGGGGAGTGGTGACGGCTGCCGGCATGGTTCGCCGTTACCATGTCGTTCTTCAGCGATTTTGCGAATTATTGGTCAGATCGGTACCACCATCGCCTTCCC

### Clone Rv124

ACGCCGATGAGCTGACCGAGGTCGACAGCGCCGTGTTGGCTGACTTGGAACCGACATGGAGTCGCCCCGGTTGGCGTCACCTCAAGCATTTCAATGGTTATGCGACCAGTTTTTGGGTTACGCCGTCAGACATCACGTCGGAGACTTGGATGAGCTGTGTCTGCCAGATAGCCCCGAATCGGGACCACCGTGGTCACCGTGGTCACCACTCGGGTCGGGTCGCCCGCGCTATCGGCATGGGTGCGTTATCACAGCGACACCGCGCCTGCCCAAGGANGTNCGGNCGGACC

Clone Rv126

CTTGATTTTGATCATCATGACGATCATCACCCTAATTTTGCTACCCGCACTGGTTATCGTGGGTACCGTCGTGCTTTC
CATGGGCGCCTCTTTCGGGCTTTCCGTATTGGTCTGGCAGGACATTCTGGGTATCGATTTGTACTGGATGGTGTTGGC
GATGTCGGTGATCCTGCTCCTGGCGGTGGGATCCGACTACAATCTGCTGCTGATTTCCCGGTTGAAAAAGGAAATTGG
GGCCGGATTGAACACCGGAATTATCCGTGCCATGGCTGCTGCTACCGGGGGAGTGGTGACGCCTGCCGGCATGGTGT

GGGGATCCCTAGATCGACCTGCAGGCATGCAAGCTTGGCGTGTCGTTCCAACCCGAATTGGCTTTCGGCGCCATCGGT
GAGGCGGGACACACCTCGATGCTGCCGCCATGGACGCGGTCGAACGCAAGCAGCTGATCGAGCTACAACGCCGCGCG
AACGCTTCCGCCGCGGGCGTGACCGCATCCCGTTGACCGGGCGGATCGCGGTGATCGTCGATGACGGCATCGCCC
GAGCNACTGTCAAGGCGGCGTGCCAGGTCGCCGGCGCACGGTGGTGGTGTTCTTCGCCG
CAGACGACATCGTGGCGAGATTCGNCGGGTACGCCGATGAGGTGGTGTTTTTGGCGACGCCGCGTNGTTCTTCGCCG
NCGGGCANGGTTACCGCAACTTCACCCAGACCTCCGACGACGACGTGGTGGTGTCTCCTGGATCGTGCTC

Clone Rv127

AAGGCTGCAGGTCGAAGCGGNTGGTTACGACTCCCTGTGTGTGATGGACCAGTTCTACTATCTGCGTCTACACGGCCC
TTGGTGCGCTGGCCACGGCGACCGACCGACCGCTGCAAGCCCCGACCCTGCCAAGCCAAGCACACACCACGCCAAGCCCCGACCCCGCCAAGCACACACACACACGCTCGACCTCGCCAAAGATNATCACCACGCTCGACGTGGTTAGCGCCGGTCGAGCGATCCTCGGCATTGGAGCCGGCGGGTTT
GAACTGGAACACCGCCAGCTCGGCTTCGAGTCCGGCACTTCCAGTGACCGGTTCAACCGGCTCGA

CTTTCCGCGGTACCCGCTCAACTTTGTGTCGACCCTCAACGCCATTGCCGGCACCTACTACGTGCACTCCAACTACTT
CATCCTGACGCCGGAACAATTGACGCNGCGGTTCCGCTGACCAATACGGTCGGTCCCACGATGACCCAGTACTACAT
CATTCGCACGGAGAACCTGCCGCTGCTACAGCCACTGCGATCGGTGCCGATCGTGGGGAACCCACTGGCGAACCTGGT
TCAACCAAACTTGAAGGTGATTGTTAACCTGGGCTACGGCGACCCGGCCTATGGTTATTCGACCTCGCCGNCCAATGT
TGCGACTCCGTTCGGGTTGTTCCAGANGTCAGCCCGGTCGTCATCGCCGACGCTCTCGTCN

Clone Rv128

Clone Rv129

GCGAAAGTCCGTTGGGTGCAATGATGTAGCGCTTCTCCCCATCGAGATAGTGGAGCAACGCAATCCGTGCGGTACGGT TCGGGTCGTACTCGATGTGCGCGACCTTGGCGTTGACACCATCTTTGTCATTGCGGCGAAAGTCGATCATCCGGTNNG

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### Clone Rv130

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### Clone Rv132

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### Clone Rv134

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GCTTCCGGCTCGTATGTTGTGGGAATTGTGACCGGATACCAATTTCACACAGGAAACAGCTATGACCATGATTACGC CAAGCTAGTTAGGTGACCATGATTACGC CAAGCTAGTTAGGTGACACTATACAATACTCAAGCTTGCCGGCTGGTGGGCCGACCACTTCGATGGCACCGTGA ACTGCTGCCCGGCCAATTCTTCTTGGTCGCCCGGACCGATGGACCGCGGCTGGGATTCCAGAAGGTGCCCGATCCCGC CCCTGGGAAAAACCGCGTGCACCTCTACTTCACGACCAACGAC

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Clone Rv135

Clone Rv136

Clone Rv137

TTCCAACCCTAATTGGCTTTCGGCCCCATCCGTGAGGACGGGGTGCGGGTGCTCAACAACAACGTCGTCCGCGGGACA
CACCTCTATGCTGCCGCCATGGACGCGGTCCAACGCAAGCAGCTGATCGAGCTACAACCCCGCGCGGAACGCTTCCGC
CGCGGGCGTGACCGCATCCCGTTGACCGGGCGGATCGCGGTGATCGTCGATGACGGCATCGCCACCGGAGCGACGGCC
AAGGCGGCGTGCCACGTCGCCCGGGCGCACGGTGCGGACAAGGTGGTGCTGGCGGTCCCGATCGCCCAAACGACATC
GTGGCGAGATTCGCCGGGTACGCCGATGAGGTGGTGTTCTTCGCCCTCGGGCAGGGT
TACCGCAACTTCAC

Clone Rv138

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Clone Rv139

GTTTATGCACTGGTTAGGTGTTTCCATGAGTTTCATTCTGAACATCCTTTAATCATTGCTTTGCGTTTTTTATTAAA
TCTTGCAATTTACTGCAAAGCAACAACAAAATCGCAAAGTCATCAAAAAACCGCAAAGTTGTTTAAAATAAGAGCAAC
ACGTACACAAGGAGATAAGAAGAGCACATACCTCAGTCACTTATTATCACTAGCGCCGCCGCAGCCGTGTAACCGAG
CATAGCGAGCGAACTGGCGAGGAAGCAAAGAAGAACTGTTCTGTCAGATAGCTCTTACGCTCAGCGCAAGAAGAAATA
TCCACCGTGGGGAAAAACTCCAGGTAGAGGTAC

Clone Rv13

ATACTCAAGCTTGGGTGTAGCCGATCACCGGAAGTCNCATGATCAGCCACGTTCCGCGCCCCGGCATACGGTGGTG TACCGATCTCCGCGTCATACACCCGCGGGTAATCGCCGACGGTGCCGGTTCGCGAGCCGAA

Clone Rv140

Clone Rv141

AATATTCAAGCTTTCGGCGGAAACGGACNCCTTGCGAACATTGATAACAAAATAGAAATCATTGATGGTTTGAGTCAC CAGGCCGATCAAGCCTTCGCCGAGCCCAAATTCCAATCAAGAGGCCCAAGCCCGTACCAATCAGCCCGGCAACGAGGGA TTCCGTCNTTATCAGCCNAAATAACTGCTCTCGGGTACCACCCCAAACAGCGCCAATATGGCGAAAAACGGTCGCCGTTG CACAACATTAAATGTCTCGGTATTGATTAAAAAGATACCCACCACCAGGGCAATCCAACTGAGAGCGGTTAAATT GACCGTAAAAAACCTCCCGTCATCTTT

CAGGCATGCAAGCTTGCTGCATCTTCCTGTGACTGCTCCCGAAACCTGGGGGTGTGCCTGCTGTTGTATGCACGGCATA CGGCATGCATGCACCTTGCCTGTTCCTGTGAACCAGGCCACGCCAAGCCCACGTGTCCATCATCAGGGGTCAACCCCGGCCAAGGGCGAC GGCACGCCAAGTTCGCCGACCGTTAACCTAGTGCTGTTAGCTTCATTTGCTGCGAGCAAAACAGCTGGTCGGCCGTTA GGAACTGAATTGAAACTCAACCGATTTGGTGCCGCCGTAAGTGTCCTGTCTGCGGGTGCGCTGTTTGTCCGCGTGT GGTAACGACGACAATGTGACCGGGGGGAGGTGCAACCACTGGCCAGGCGTCCGCGAAAGTCCATTGCNGGGGGAAGAAG ACAC

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Clone Rv142

GAAAGTGCCCCAAGGTGTTGGTGAAACTCGCTGGACGGTCCCCAGGATGTTGGCAGCACATTCACCGGACATGACCGG
AGCAAGACCGGACATCCTCCCATACCGTCGCCGTGTACATCCGTAGCCCGTCCTGGCAGGTGCTGGGTTGAACAA
AATCAGCCCAACACCTGCCACGACGAAGAAGCGGGTTGCGCTGGCATGTCTTTGTCGGCTCGGCGATCGAATTCTACGA
ATTCCTTATCTACGGGACCGCTGCGGCGCTGTTTTCCCACCGTGTTCTTCCCACACCTGGATCCCACGGTGGCCGC
CGTGGCCTCCAAGGGGACATTTGCTGTGGCGTTCCTATCCCGGCCGTTCGGCGCGCCGTCTTTGGATACTTTGGAGA
CCGCCTCGGCCGCCAGAAGACCCTGGTCGCCACACTGTTGATCATGGGCCTGGCAACCGTGACTGTTGGGCTGCTTCC
ACGACAGTGGCCATCGCGC

Clone Rv143

Clone Rv144

ATACTCAAGCTTCCCGGCCGCAGGTGACGGCGCGCCTAGCGCCACTTGATGCCGCACCCGATCGACGGNCGTTGGTC
GGGGTTGACTGGCCGCCCGCGCGAGCAGGGCGTCAACCGGGCCGGACGTCGGCGGCCGTCACCGGTCGGCCATTGCC
CGGGCGGAGTCGTCGAGCTGACCACGGTAGACAAGTCGGCGCTCGCAGCAAAACGTGTCGGGTGTGCAGGC
CGCGGAGAAGGCCCNGGCGACGTCTCGGGTTTCGTCGTAGAGATACGGGAACGTCCAGCCGTGGCGGGGCCTCGGC
GACCATCTGATCGGGCCCGTCCTGCGGGTAGGTGACCACGTCCTTACTGGAGATACCGACCATCGGGACCCTTTGATC
GGCGAGGTCCCGGCCGACCGTGGCCAATCCGGCGGCGACGTGTCGCCCGTACCGGCCAGTGGTTC

49

 ${\tt CAGGCATGCAAGCTTCATGCCCGCGGCATGATAGCCACATGCACGCAATCGAACTCAGCGAAACCGGCGGGCCAGGCGTCTTACGCCACCTCACCAGCGCGAACCTCAACCCGGCCACGGAGACCTCCTGATC}$ 

Clone Rv146

CAGGCATGCAAGCTTGGCGTGCCGTTCCAACCCGAATTGGCTTTCGGCGCCCATCGGTGAGGACGGCGTGCGGGTGCTC
AACGACGACGTCGTCCGCGGGACACACCTCGATGCTGCCGCCATGGACGCGGTCGAACGCAACGCAGCTGATCGAGCTA
CAACGCCGCGCGGAACGCTTCCGCCGCGGGCGTGACCGCATCCCGTTGACCGGGCGGATCGCGGTGATCGTCGATGAC
GGCATCGCCACCGGAGCGACGGCCAAGGCGGCGTGCCAGGTCGCCGGGCGCACGGTGCGGACAACGTGGTGCTGGCG
GTCCCCATCGGCCCAGACGACACTCGTGGCGAGA

Clone Rv147

TAGTCGCTGACCGGTGCAGGTTTCGACNATGTGGTGCCGGTTCGGCGGCTACGTGCCATCGAGACACTGGCGCAGGCT
ATCGCACCCGTTATCGGCTACGAGCAAATCGCGGTATGCGTTCTTGAGCATGAGTCGGCGACCGTCGTCATGGTCGAC
ACCCACGACGGAAAGACGCAGATCGCCGTCTANCNTGTGTGCCGCGGATTATCAGGACTGACCTCCTGGCTGACCGGC
ATGTTTGGTCGCGATGCCTGGCGCCCGGCCGGCGTGGTCGTCGTCGGCTCGG

Clone Rv148

Clone Rv149

ATACTCAAGCTTTGGCATTGTGCACATTTTCCACCCGTGCTCTATTAATGCTGAGCCGCTAATTGTGACCCCAGTCGGGAAACACGCGGAGCACCAAATTCACCGCAGCGGCCGGGGCGGTTCAACTCACCATGGATCGCTCTCGTCGTCTGTGGTGCTGGACAATCGTCGCTGTAGCGCGTCGCGAACACCTCAGCTTCTGCTGCCGCGGCTTCTTCCGGCGATGGTAACCCCCAGGTTTCGCCCCACGGTCTTACGTAGCAGTGCGACGCGGTGTTCATCTGCATCGACCTGTTGACTCATCCTGTCAAGGATGAAGGCGTACTGGGCCGACTGCGCCACGGTCTCAGCACTCCACCAGGATCTCAGAAACGAGCTGCGACTCACCAGGCCCACCTGGCCGAAAGCTCGACATGGTCAATCCGGCCG

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Clone Rv14

Clone Rv15

CAGGCATGCAAGCTTCCACATGTACGGATCCACGAACATCCCGTTGAACTGACAGGTGCGGCCCGGCTCGATCAGGCC
GGCCACTTGTTCTACGCGGTTACCGAAGATCTCTTCGGTGACCTGCCCGCCGCCGCCAGCTCGGCCCAGTGCCCGGC
GTTGGCCGCCGCGGCGACGATCTTGGCGTCCACGGTGGTCCGGGTCTTGCCCGCTAGCACGATCCGCGAGTCGGCCGG
TCACCCGGGT

Clone Rv151

Clone Rv152

Clone Rv153

Clone Rv154

ATACTCAAGCTTGATCTTGATCATGATGATGATCACCCGAAGTGTGGTAGCCGCAGTGGTTATCGTGGGTACCGT
CGTGCTTTCCATGGGCGCCCTCTTTCGGGCTTTCCGTATTGGTCTGGCAGGACATTCTGGGTATCGAGTTGTACTGGAT
GGTGTTGGCGATGTCGGTGATCCTGCTCCTGGCGGTGGGATCCGACTACAATCTGCTGCTGATTTCCCGGTTGAAAAA
AGAAATTGGGGCCGGATTGAACACCGGAATTATCCGTGCCATGGCTGGTACCGGGGGAGTGGTTACCGCTGCCGGCAT
GGTGTTCGCCGTTACCA

ATTGNCTTTCGGCGCCATCGGTGAGGACGGCGTGCGGGTGCTCAACGACGACGTCGTCCGCGGGACACACCTCGATGC TGCCGCCATGGACGCCATCGAACGCCAAGCAGCTGATCAACGCCGCGGGAACGCTTCCGCCGCGGGCGTGA CCCATGGACGCGTTGACCGGTTGACCGGTTGACCGGGCGATCGCCGTTGACCGGCGAAGCGGCGAAGCGGCGAAGCGGCGAAGCGCGTG CCAGGTCGCCCGGGCGCACGACGACAAGCTGGCGAGATT CGCCGGGTACGCCGATGAGGTGGTGTTTTTGGCGACGCCGGCGTTGTTCTTCGCCGTCGGGCAGGGTTACCGCAACTT CACCCAGACCTCCGACGAAGAAGAGTGGTGGCGTTTTCTGGATCGTCCTC

Clone Rv155

GCACGGAGAACCTGCCGCTGCTAGAGCCACTGCGATCGGTGCCGATCGTGGGGAACCCACTGGCGAACCTGGTTCAACCAAACTTGAAGGTGATTGTTAACCTGGGCTACGGCGACCCGGCCTATGGTTATTCGACCTCGCCGCCCCAATGTTGCGACCTCGGTTCGGTTGTTCCCAGAGGTCAGCCCGGTCGTCATCGCCGACGCTCTCGTCGCCGGGACCAGCAGGGAATCGCCGATTTCGCCTACA

Clone Rv156

ATACTCAAGCTTGGGGTGGCGCTGTCGGTGGTTGCTTGGCGGCGTCGGTATCAACACCGCCCACGAAATGGGGCAC AAGAAGGATTCGCTGGAGCGCTGTTCCAAAATCACCCTCGCCCAGACCTGCTACGGGCACTTCTACATCGAGCAC AACCGTGGCCATCACNTCCGGGTGTCCACACCGGAGGACCCGGCGTCGGCGTTCGGCGAAACGTTGTGGGAGTTC CTGCCCCGCAGTGTTATCGGCGGCTTCGGCCTCGGCGTTCATTTGGAGGCCCAACGGCTGCGTCGGCTCAGC CCCTGGAATCCCATGACGTATCTGCGCAACGACGTGCTCAACNCGTGGCTGATGTCNGTGGTGTTTTTGGGGGTGGGC

TCGCCACCGCACCGCGGCGAACGCTCAAAGGCACCTACTGGCACCAAGGCCCCACACGTCACCCTGTGACCTCCTGCG
CCGACCCCGCCCGAGGTCCTGGCCGTTACCACCGAACGGGCCGGGGAGTCTGGTACGCATCGAACAAAGAGCAAG
GTGCATGGGCGGAGTTGTTCCGCCACTTCGTCGATGACGGGGTCGATCCATTCGAGGTCCGTCGCCGCTCGGTCGAG
TGGCGGTCACACTCCAGGTACTCGACCTCACAGACGAGAGACTCGATCCCATCTAGGTGTGGACGAAACAGATCTTC
TGTCCGACGACTACACCACCACCAGGCCATCGCCGCCGCGCGGATGCCAACTTCGACGCCGTACTGGCCCGGCGG
CGGCGCTCCCCGGGTTGTCAAACACTTTGCCGTGTTCACGCACTGCCCAACATCGAGCCCGA

Clone Rv157

Clone Rv159

GGTATAGTCGCTGACCGGTGCAGGTTTCGACAATGTGGTGCCGGTTCGGCGGCTACGTGCCATCGAGACACTGGCGCA
GGCTATCGCACCCGTTATCGGCTACGAGCAAATCGCGGTATGCGTTCTTGAGCATGAGTCGGCGACCGTCGTCATGGT
CGACACCCACGACGGAAAGACGCAGATCGCCGTCAAGCATGTGTGCCGCGGGATTATCAGGACTGACCTCCTGGCTGAC
CGGCATGTTTGGTCGCGATGCCTGGCGCCCGGCCGGCGTGTCGTCGTCGGCTCGGATAGCGAGGTCAGCGAATTCTC
GTGGCAGCTCGAAAGGGTCCTGCCGGTGCCGGTCTTTGCGCAAACGATGGCGCAGGTTACGGTCGCGCGGGGTGCGGC
CCTGGCGGCGCCCCA

Clone Rv15

GACACTATATNATACTCAAGCTTCAGGTCAATGTGCGCCAAGCCCTGACGCTGGCCGACCAGGCCACCGCCGGAN CCCTNTCTAGA

CTGTAGCCACCTGTTGCCATCCCCGTCATGCCCGACTCTGGTCATCTCGGATCCGCTGACACCCCGCTAAGGCTGCTC
CTCTCGGTGCATTACCTCACCGACGGCGAACNCCCCCAGCTTTACGACTATCCGGATGACGGCACCTGGTTGCCGGCT
AACTTCACCGTCAGCTTGGACGGCGGCGCTACCGTCGATGGCGCCAGCGGGCCGGGCCCGGCGACCGATTC
GTCNTCANCCTGTCGCGTGAACTTGCCGACGTCATCGTGGTCGGTGTGGGCACCGTGCGCATTGAGGGCTACTCCGGC
GTCCGGATGGGTGTCGTCAAGCGCCCGCACCGGCAGGCCCGA

Clone Rv160

Clone Rv161

ATACTCAAGCTTGGGTGTTGCCGATCACCGGAAGCCGCATGATCAGCCACGTTTCGCGCCGGCCATACGGCGGCG
TACCGATCTCCGCGTCATACACCCGCGGGTAATCGCCGACGGTGCCGGTTCGCGAGCCGAAGGTGACGACGCTGATTG
AATCGAGTTCCAGGGCGCGGGTGGCGCAGCAACGGCGCGAGCTCAACNACGTCAATCACGTTGTCGCTTTCTACGG
TCACCGACCCGGTGACCGTAGTCGCCCGGTGCGCTCGGCCGAGAAGTTGCACCGCCACCACCGCGACAACGTCTTGCA
CGCGGACGCCACCCCCCGGAT

GCGCNAACAGCTCGCGGCAGCCCACGACGTGCTGCGTCGGATTGCCGGCGGAGATCAATTCCAGGCAGCTCCCGGA CAATGCGGCTCTGCTGGCCCGCAACGAAGGACTCGAGGTCACCCCGGTGCCCGGGGTCGTGGTGCACCTGCCGATCGC ACAGGTTGGCCCACAACCGGCCGCTTGATGCCCGGTCGGCAAGCCCGGCAGTTGCCAAACCCAGCGTGATCAGGCTCG GCTCGCGAGTTCGGCGAAAAAGTGGCTCGCCTGATCACCTACCATCGGCCAGGATCTGCGTGTCATCACGACGCTCGC CAAGGAGGTTGTTGTGGTGCTATCGACGGCCTTTAGCCAGATGTTCGGAATCGACTATCCGATAGTGTCCGCGCCAAT GGACTTGATCGCCGGCGGTGAGCTGGCTGCCGCNGT

Clone Rv162

ATACTCAAGCTTTCTCCGATACCCGCCATGTCGCGCACATCCAGGACTTCTGGGGGGGATCCGCTGACAGCGGCGGGATCCCAAAGTGCGGATGATCGGGCCGCCTACGTCGTGGTGTACCTCGTCGGTAACAACGAAACCGAAGCGTATGACTCGGTCACGCGGTGCGGCACACGCGCCACCGCCACCGCCACGGGGTGAAGGCCTATGTCACCGGTCCGGCAGCACTCAATGCCGACCAGGCCGAAACAAAAGTATCGCTAAGGTCACCGCGATCACGAACATGGTGATCGCAGCAATGGTTGCTAGTGATCGCTCCG

::::::::::::::::::Rv162T7.seq:::::::::::

Clone Rv163

CCAAGATCTACACCATCGAATACGACGGCGTCGCCGACTTTCCGCGGGTACCGCTCAACTTTGTGTCGACCCTCAACGCCATTGCCGGCACCTACTACGTGCACTCCAACTACTTCATCCTGACGCCGGAACAANTTGACGCAGCGGTTCCGCTGA

CCAATACGGTCGGTCCCACGATGACCCAGTACTACATCATTCGCACGGAGAACCTGCCGCTGCTAGAGCCACTGCGATCGTGCCGATCGTGGGGANACCCACTGGCGAACCTGGGTTCAACCAAACTTGAAGGTGATTGTTAACCTGGGCTACGGCGACCCGGCCTATGGTTATTCGACCTCGCCCCCAAATGTTG

#### Clone Rv164

AGCTTCCCGAGTTCGGCTTTGGATCAAGACCCCAGTCCGCGGCGCGCGATCCGGCNGCTCGGTGACTACATCAAGCCAC
AAATCGACGGCTTTCGGGGTGCCGATACCGATGACGTGGCGGATGTCGAGTGTTGAGTTCTCGGCGGGGCGGATGCTC
ACCTGGCGATCACCTGCCTCTCGTTGACGATCGATCGTCTATGCCGCCGTCTCTGCGGGAACAGGCCNCCAGTACATC
GCCACAGACGGGATCCACCCGCATTTCGGCTACGGTTGCTCGTTTCGGTGTTCGGACTAGTCGGTCCTGGTGACGTGC
CGGTGATGCGGACCGGTCCTAGCACTGACCAAATGCGGGC

CGGGGGGCCTCTTAATAGTGTAGGAAAGAAGCTCTACATATTCAGGAGGATTCACCATGGCTCGTGCGGTCGGGATCG
ACCTCGGACCACCCAACTCCGTCGTCTCGGAAGGTGGCGACCCGGTCGTCGTCGCCAACTCCGAGGGCTCCA
GGACCACCCCGTCAATTGTCGCGTTCGCCCGCAACGGTGAGGTGCTCGTCGCCAGCCCGCCAAGAACCAGGCAGTGA
CCAACGTCGATCGCACCGTGCGCTCAGGCGACACATGGGCAGCGACTGGTCCATAGAGATTGACGGCAAGAAAT
ACACCGCGCCGGAGATCAGCGCCCGCATTCTGATGAAGCTGAAGCGCCGACGCCGAGGCCTACCTCGGTGAGGACATTA
CCGACGCGGTTATCACGACGCCCGCCTACTTCAATGACGCCCAGCGTCAGGCCCACAAGGACCCGGCCAGATCGCCGG
TCTCACGTGCTGCGG

### Clone Rv165

CTGGTGCTGGACGGAGCCTAGTACAACTTCCTCTCCAATGCTCTTGCCCCGATCGCGGCCACCAGGATGACCCAGGACACTGCTGGACACACCCGAGACACCCGAGACACCCGAAGTACTGGAAAAAGCTCACACCCGAGTTCGTCGCACCGGTGGTGGCCTACCTGTGCACCGAGGAGACGCCGACAACCCATCGGTGTACGTCGTCAGTGGTGGTTAGGTGCAGCGAGATTGCGCTGTTTTGGCAACGACGCGCCCAACTTCGACAAACCCGCCGTCNGTACAAGATGTTGCGGCGCGGTGGGCCGAGATCNCCGATCTGTCCGGTGCGAAAAATTGCTGGATTCAAGTTGTAGAACTAAAT

### Clone Rul66

ATACTCAAGCTTTTCCGGCGTCGTCCACCTGACCCAAAAAGCGCAGGTGCGCCGAAACGGCCCGCCTGGCCGCCAACCGCTCGCCGCACCACCTTCGGCACCACCACCTTCGGCAGCGCGCAAACCGCTGCACCACCCTTCGGCAGCGCGTCAAGCAAAAACGGCCATTCC

### Clone Rv167

GTGTGCTGTCAATTCAGAGCTGAGCCTGATGCACTCAACTTACTGAGCATGCTAACGCTGGTCGTGCGGGTCTTGTTCCCGCGTGTCGGCAGGGCACACGCTCGGGGCGTAGCTGGGAGAGGCCCCGGTCAAGCCCGGAGAGCAGTGCTCAGTCCG

### Clone Rv169

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### Clone Rv16

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CCGCTATCGGTCGGTGTGCTTGGCGGCGTCGGTATCAACACCGCCCACGAAATGGGGCACAAGAAGGATTCGCTGGAG
CGGTGGCTGTCCAAGATCACCTCGCCCAGACCTGCTACGGGCACTTCTACATCGAGCACAACCGTGGCCATCACGTC
CGGGTGTCCACACCGGAGGACCCGGCGTCGGCGCGGTTCGGCGGAGACGTTGTGGGAGTTCCTGCCCCGCAGTGTTATC
GGCGGCTTGCGCTCGGCCGTTCATTTGGAGGCCCAACGGCTGCGTCGGCGTCAGCCCCTGGAATCCCATGACG
TATCTGCGCAACGACGTGCTCAACGCGTGGCTGATGTCGGCTGGGTGTTTGTGGGGTGGGCTGATCGCGGTCTTCGGCCCG
GCGCTGATCCCGTTCGTCATCATCCAGGCAGTCTTCGGCTTCAG

# Clone Rv170

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ATACTCATGCTTGCCGAAGTTCCGATGGGTCGCCGCCGANCCCAGCGAAGTCGCTAGCGTGGCCGTGTTCTTGGCT TCGGATCTATCCTCGTACATGACCGGCACCGTGTTGGACGTGACTGGCGGCCGGTTCATATGACACCGAGATCATTGC CACGGTACGGCAATTCGTCAAGAAGGAAATCTTTCCCAATGCACCGGCCCTCGAACGTGGCAACAGCTACCCGCAAGA AATCGTCGATCGGCTGGGTGTTATTGGCTTGCTCGGTCGCCGGCTGCAAGGGTATCGACACCACCGAGTTCATTCTCC GGGCGTGCC

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Clone Rv171

:::::::::Rv171SP6.seq::::::::::

ATACTCAAGCTTCGGCCTCGCTGCAGGAGTGGGAGCCGCAGGGCTGGAAATCCGAAAAACGAGCCGGTGATCGCACTG
TCGCCGATCGGGGCCGCCCCGGTTGGTTACCGATGAATCCGCACCCAAAATGTGGCTGCGGTGGCGTTTCTTGAC
TCCTTGGCGTCGACTCTTGTGGCAGCCACCGAGCGGTTGGTCCAGGATCTGGATGGGCAAAGTTGTGCGGCCCGGCCG
GTGACGGCCGATGAGCTGACCGAGGTCGACAGCGCCGTGTTGGCTGACCGACATGGATTCGCCCCGGTTGG
CGTCACCTCAAGCATTTCAATGGTTAT

Clone Rv172

Clone Rv173

CATCGTCGAACTTCGGTCCGGGTTGNTAGNACCGCAGCACCAAACGCACCCACCGACCCCCACGCTTCACGCCAACCC
TTTAGTTCATTGGCGTGAACAGCAGCGTAGCCGGTTGCCCCGATATATGTGGAAAAATCGTTCGGACGTACAAAAAAA
GTTCCTGACGCTGGCGTCAACTCGAAACTGCCTCGGAAGTCAATGATGATCATCAGTCAATATTAAAGTCG

Clone Rv174

Clone Rv175

CGCCAATTCACGATATCCTTAACCGATATCCCGAGCCGATAGCTGGCGGGCTCGGGTGGTGGCCAGCGGCGCTGCGACGAAAGGTGTGACCGTCATGAAACAGACACCACCGGCGGCGGCCGTCGGCCGTCGTCACCTGCTCAGCATCTCAGCATCCGC

AGCCGGTGTGATCGCGCTTTCGGCGTGTAGTGGGTCGCCGGCCCGACCCCGGCAAAGGCCCGGCCCGACACACCCCGGAACAGGCAGCCCGGAACACCCCGGAACACCCGGAACACCCGGAACACCCGGAACACCCGGAACACCCAAACGCATCCTGCTGAT

### Clone Rv176

# ::::::::::Rv176SP6.seq:::::::::::

ATACTCAAGCTTGGGCACTGACTTCGGTACCCCCTCCGCCTTTGGCCAGCAGCAGCCACAGCGGGGTTCGCGGACCGA ACGTGGACATCAATAGCCCGGAATCGGTGTGTGCAAGTTGGTAAACGGTGTTGATCCCAAGCTTTGCCAGCCTTTTCG TAGTCTTGGGCCCCACACCCCACAGTGCTTCGACGGTACGGTCACCCATGATGGCCATCCAGTTGGCATCGGTGAGCT GATAAATGCCAGCTGGTTTCGCCAACCCGGTAGCGATCTTGGCGCGCTGCTTGTTGTCACTGATACCTATCGAGCAAG ACAGCCCGGTTTGCGACAAAATGACTTTTCGGATCTCTTCGGCGACTTCGATGGGGTCGTCGGGA

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AAAGTCCTGTGCCGGTTCGCTAAACACCCGGCGGACACTCAGACGGTGCTGGTGGTGCGGCATGGCACCGCGGGCAGC AAAGCGCACTTCTCCGGGGGACGACAGCAAGCGACCGCTAGACAAGAGGGGTCGTGCCAGGCAGAAACGTTGGTACA CAGCTGCTGGCGTTCGGCGCCACCGATGTTTATGCCGCCGACCGGTGCGCTGCCACCAGACGATGGAGCCACTCGCC GCGGAACTGAACGTGACCATACACA

### Clone Rv177

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ATACTCAAGCTTGGGTTCCACGCCGCGCAGCCACGCCGTCACCTTTCCACGAGACCTCACCTGCCGATCCGAAATGG
AATCGGCCGTGACGGAATTGGCGCACCGAACACCCAACGAGGTGGTGGCTTCGTCGCGAACCGTCACCCGAGTCGCGG
CCACCGTGCGCACGGCGCACGTTCTACACCCGCACCAAGATCCGAAAGCTGCAAGCTCCCAGCACCGATCCCGACGTCA
TCACCGCTGCCGCCCGGCACGTCCTTGACCTATTCGAGCTGGATCGGCCCGTCCGGTTGCTGGGAGTGCGGTTAGAAC
TGGCCTAGAACCGGCGGGCACACCGCNCCTGGGCGGGCGAATTCTTGACCGCNCCGGCC

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### Clone Rv178

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### Clone Rv179

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### Clone Rv17

Clone Rv180

Clone Rv181

Clone Rv182

CTCAAGCTTGGTGCCGACATGGCCGGGCTGGAGCCCGCGTATGGCAAGGTTCCGCTCAATGTGGTTGTGATGCAGCAG GACTACGTTCGCCTCAATCAGCTCAAACGTCACCCCCGTGGCGTGCTGCGCAGCATGAAGGTCGGCGCCCGCACGATG TGGGCGAAGGCAACAGGTAAAAACCTGGTCGGCATGGGTCGAGCCCTCATTGGGCCGTTGCGGATCGGGTTGCACCGC GCCGGAGTGCCGGTCGAACTCAACACCGCCTTCACCGATCTTTTCGTCAAAAAATGGCGTCGTGTCCGGGGTATAC

CCGAAGCGTGGGAAATCCTGACCGAATACCGCGACGTGCTGGACACTTTGGCCGGCGAGCTGCTGGAAAAGGAGACCC TGCACCGACCCGAGCTGGAAAGCATCTTCGCTGACGTCTAAAAGCGGCCGCGGCTCACCATGTTCGACGACTTCGGTG GCCGGATCCCGTCGGACAAACCGCCCATCAAGACACCCGGGGGAGATCGCGATCGAAACGCGGCGAAACTTGGGCC

Clone Rv183

GCGGTNTAGCTTCCCGTCGTACCGGCGACCGCCAGCCGAGAAGCTCGTTTTCCCAGTGTTGCTGGGGATTCTCACGCT
GCTGCTGAGTGCGTGCCAGACCGCTTCCGCTTCGGGTTACAACGAGCCGCGGGGCTACGATCGTGCGACGCTGAAGTT
GGTGTTCTCCATGGACTTGGGGATGTGCCTGAACCGGTTCACCTACGACTCCAAGCTGGCGCCGTCTCGTCCGCAGGT
CGTTGCTTGCGATAGCCGGGAGGCCCGGATCCGCAATGACGGATTCCATGCCAACGCTCCGAGTTGCATGCGATCGA
CTACGAATTGATCACCCAGAACCATCGGGCGTATTACTGCCTGAAGTACCTGGTGCGGGTCGGATACTCCGGC
GGTGACGACCCCCGGCAAGCCGCCATCCGTGCTGCTGT

Clone Rv184

::::::::::Rv184SP6.seq::::::::::::

Clone Rv185

::::::::::Rv185SP6.seq:::::::::::

::::::::::Rv185T7.seq:::::::::::

Clone Rv186

:::::::::Rv186SP6.seq::::::::::

CGTCCTTTTCCCCAAGATAGAAAGGCAGGAGAGTGTCTTCTGCATGAATATGAAGATCTGGTACCCATCCGTGATACA
TTGAGGCTGTTCCCTGGGGGTCGTTACCTTCCACNAGCAAAACACGTAGCCCCTTCAGAGCCNNATCCTGAGCAANAT
GAACAGAAACTGAGGTTTTGTAAACGCCACCTTTATGGGCAGCAACCCCGATCACCGGTGGAAATACGTCTTCAGCAC
GTCGCAATCGCGTACCAAACACATCACGCATATGATTAATTTGTTCAATTGTATAACCAACACGTTGCTCAACCCGTC
CTCGAATTTCCATATCCGGGTGCG

Clone Rv187

CTCAAGCTTCATGTCCGTACGGCTCGGGTACGCTTCCGTCGCAGTGTGCGAGTGATAAATGACGACCGGGACCTCGTCGGCATCTTCCATAGCCCGCCACACCTTCAGTTGCTCACCGGAATCCAACCGGTAGAAGGTCGGCGAGCGCTCGGCATTGGTCATCGGGATATGCCGCTCGGGACGGTCAGAGCCCTCGGGTCCGGCCAGCACTCCGCAGGCTTCGTCGGGGTGGTCGCACACGCATGGGCCACCATCGCATTCAC

### Clone Rv188

CGCCACGTTCATGGGCAACACCCCGATCACCGGTGGAAATACGTCTTCAGCACGTCGCAATCGCGTACCAAACACAT CACGCATATGATTAATTCGTCCAATTGTATAACCAACACGTTGCTCAACCCGTCCTCGAATTTCCATATCCGGGTGCG GTAGTCGCCTGCTTTCTCGGCATCTCTGATAGCCTGAGAAGAAACCCCAACTAAATCCGCTGCTTCNCCTATTCTCC AGCGCCGGG

# Clone Rv189

::::::::::Rv18SP6.seq::::::::::

ATACTCAAGCTTCAACCGATTGACGCATTGTGCGAACTGACGGCGCCCGCGCATGGCCAATCCGGAAGACCATCATTG
GCCAGTGGCCGGGCGCTAACAGGTTCCAGCCCCCACCAGTGCCGCTCGAACATGCGGTGCAACCCATTCGCAGGCCG
GCAGGGAAAGCACCGCGGAAGCCGCAAAGGGCTGCAGTTCCGCGCCCCAATAGTGTCGTCCGCAACCAGATGCGCTCGA
AAACCGCGCCGGCAGTCAGCGCACCCGACGCGAGGTCGAGAGACCTCGTCAGCGCGCCCACATGGGGTGCCAATCGGC
ACGCCAGGTAGGCCGCGCAACCCGAACGCGTGGTGCATGCCCACGGTCCGCAGGAGGCGCAACCCGCCAATGCC
GAAGCCCACGAAACATCGGGCGCATCCACGCTTCAACCTC

#### Clone Rv18

# Clone Rv190

::::::::::::Rv190SP6.seq:::::::::::

CCTTAAGCCCCGCAGGGCCCGCACGCGCGGTACCGCCCAGGTCGCCCAACAGATCGTCGATGTTCGCGTCGTCCGCC
TCGCGCACGTGGTCTGTCACCAGTCAACGTTAACGCCGCCGCACATGTCCTGCGGCCGGGCAAAAACGTGAAAAACGA
GCGGGCGACTGCAATGTCATGACACCGACGGCCGCCGATGGGCCCAGGGTCTGGCAGATTCGATCTGTGCGGCCAGTG
CCAGCAGCGTCGCCTCGTCATACGGCCGGCCGACGAGTTGAACCGACATGGGCAGGCCGTCGCCGTCGAAGTCCCACG
GCACCACGGCCGGGGCTGGCCGGTCAGATTCCAGACTTGAAAGTACGGAACCCGCTGCACCACCAGCAGCAACGTCG
AAACTGCACCCCGGCGTTGGTAGGCGCCGATGCGGGACGGGCCGGTCGCGCGCCTGGCGTCACAACTACGTCGACAT
CGTCGAAGATCGACTGGATCGGCTGCTCACACCACTCGGCGCCCAACGCCGCCCATCCGCCGTC

### Clone Rv191

 ${\tt TTGGTGATGGCGAACTTGGCCACCCGCTGGGTGTTGACATCCTCGACGGTGGGCAATTGCCCCCGGTAACGTTGCCGCCT}$ 

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### Clone Rv192

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ATACTCAAGCTTGCCGAAGTTCCGATGGGTCGCGCGCGAGCCCAGCGAAGTCGCTACCGTGGCCGTGTTCTTGGCT
TCGGATCTATCCTCGTTCATGACCGGCACCGTGTTGGACGTGACTGGCGGCCGGTCCATATGACACCGAGATCATTGC
CACGGTACGGCAATTCGTCAAGAAGGAAATCTTTCCCAATGCACCGGCCCTCGAACGTGGCAACAGCTACCCGCAAGA
AATCGTCGATCGGCTGGGTGTTATTGGCTTGCTCGGTCGCCGGCTGCAAGGGTATCGACACCACCGAGTTCATTCTCG
GGCGTGCCGGCGCATTCGAGCTGGCGGTGCGCGCTGCCCAGCACCGTCATAGGTACTTGACGATGGTCCACGTCGGAC
GAGCGCCTCCACGTCGCTGCCGAACGGTATGCATGGCGGCTACGATTCTC

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### Clone Rv193

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### Clone Rv194

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ATACTCAAGCTTGCTGCAGCTTCCTATGACTGCTCCCGAAACCTGGGGGTGTGCCTGTGTTATGCACGGCATACGGACTCCTCCATGAGACCCGCGGTCGAACCAGCCACGTGTCCATCATCAGGGGTCAACCCCGGCCAAGGGCGACGGCACGGCCAAGTTCGCCGACCGTTAACCTAGTGCTGTTAGCTTCATTTGCTGCGAGCAAAACAGCTGGTCGGCCGTTAGGAACTGAATTGAAACTCAACCGATTTGGTGCCGCCGTAGGTGTCCTGGCTGCGGTGTGGTGTGTCCACCAATGTGACCGGGGGGAGGTGCAACCACTGGCCAGGCGTCGGCGAAGGTCGATTGCGGGGGGAAGAAACACACTGACCAGTGGCCAACCACTGGCCAGGCGAAGGTCGATTGCGGGGGGAAGAAACACTCAAAGCCAGTGGGTCGACGCCAACGC

### 

AGCTTGACGCGGAGACGGACACATTGCGAACATTGATGACAAAATAGAAATCATTGATGGTTTGAGTCACCAGGCCGA TCAAGCCTTCGCCGAGCCAAATTCCAATCAAGAGGCCCAAGCCCGTACCAATCAGCCCGGCAACGAGGGATTCCGTCA TTATCAGCCAAAATAACTGCTCTCGGGTTACACCCAAACAGCGCAATATGGCGAAAAAACGGTCGCCGTTGCACGACAT TAAATGTCACGGTATTGTAGATTAAAAAGATACCCACCAACAAGGCAATCAAACTGAGAGCGGTTAAATTGACCGTAA

Clone Rv195

Clone Rv196

CCGGAAGCCGCATGATCAGCCAAGTTTCGCGCCGCCCGGCATACGGCGGCGTACCGATCTCCGCGTCATACACCCGCGGTAATCGCCGCATGATCGCCGATGATCGCGGTTCCAGCGGTTGGCGGTAATCGCCGACGGTGCCGGTCCAGCGGGTGGCGCCAGCAACGCGAGCCGAGCCAACGACGTCAATCACGTTGTCGCCTCGCTCACCGACCCGGTGACCGTTGTCGCCCGGTGCCCCGGAAAANTTGCACCGCCACCGCGAAACCGTCTTGCACNCCGGAAGCCACCCCGGATCCGTTGTTGGGCCAGGTTATTGGGT

Clone Rv19

CCGGAACCGCCGACGGCACGGTATAACGCCTCCGCATATGGGTCGACAACCAGCGGGTCGGACTTCTGGGCTTCTAGC GTTCGCGCNGTCGCGACAAACAGCGCGGTCGAACCGACACTCGTTGTGATGTCCTAGCTATCACGTTCGGTACGCACC CAATCGAGTCTAGCGCGGGTAGNTCAGCCCCGATCTCCANGCTCCGCCGAGCCAGGCGC

CTGGTTTATGTCCCGTTGAAGTTCCATCACCCGATGTGGCGGGAGCACTGCCAGGTCGATCTCAACTACCACATCCGG CCGTGGCGGTTGCGCCCCGGGGGGTCGGCGCAACTCGACGAGGCGGTCGGAGAAATCGCCAGCACCCCGCTGAAC CGCGACCACCCGCTGTGGGAGATGTACTTCGTTGAGGGGCTTGCCAACCACCGGATCGCGGTGGTTGCC

Clone Rv1

TATATAATACTCAAGCTTGCCGACGCCAACGCTCGCGCGATGTTGTTAGCCCGACCCGGCTCTTACATGGCACCGGTGCCCCACACGTCAGCCTCTGCACCGCGACCCGCTTTTACATAGAATGTGGATTGCCGGATTGCGGATGTCCGGCATCGCTCAATCTGTAGTCCGCGTTGTCCCGCGAGGGCCATGTGGATGGGGGGAAGGATCCGTGGCGTCCGGGATCACCATGGGG

Clone Rv201

ATACTCAAGCTTGCCGAAGTTCCGATGGGTCGCCCGCCGCGAGCCAACGAAATCGCTAGCGTGGCCGTGTTCTTGGCT TCGGATCTATCCTCGTACATGACCGGCACCGTGTTGGACGTGACTGGCGGCCGGTTCATATGACACCGAGATCATTGC CACGGTACGGAAATTCGTCCAGAAGGAAATCTTTCCCAATGCACCGGCCCTCGAACGTGCCAACAGCTACCCGCAAGA AATCGTCAATCGGCTGGGTGTTATTGGCTTGCTCGGTCGCCGGCTGCGAGGGTTTCTACACCACCGAGTTCATTCTCG GGCGTGCCGGCGCATTCGAACTGGCGGTGCGCGCTG

Clone Rv204

Clone Rv205

Clone Rv207

Clone Rv209

TGACACCCAACAGAGGGCACTTAAGATGGCAATGCGGCCGCCTACCTGCACGTTTTCGCGATGTCAGAGGATGCCGAGGGAGAACAATGCGAGCACGCCGCTGACNTTGCTCACCGCTTTGGCGGGCGGTGACATTGGTGGTGGTTGCCGGGCTGCNAGCCCGANTCNAGGCCGAAGCATATAGCGCGGCCGACCGCATTTCGTCTCGACCGCAAGCGCGACCTCAGCCGCAGCCGCGCCATCACGCC

 $\begin{tabular}{l} GGTGACCCCTCTATGACGCGGCGGTGGGACACTGTGATCTAAGACCGGTCTTGGGTCTTCTCCGGGCAAGGGTCTCAGT\\ GGGCGGCGATGGGCACCAATTGCTCGCCAGCGAACCAGTGTTCGCGGCCACCATCG\\ \end{tabular}$ 

### Clone Rv20

### Clone Rv214

CCGGGGTAGAACGATGCGATCTGGGCCATGTCGACATCGGTGGTACAGGTAAACCGCGCCGTGTGCGCGGTCTCGGAGATCAGAACGTGGTCGCAGTTGACACCGCGGGCTTTCAGCCAGTCGCGATAATCGGCGAAGTCGGCGCCTGCCGCCCAACTAGCACCTCGCCACCCTAGCACCCGATGGCGAAGGCCATGTTTCCGGCCACGCCGCCGCGGTGCATCATCAACTC

### Clone Rv215

# Clone Rv217

ATACTCAAGCTTGCGTTCGATGAAGTAGTCGTCGGTCAGCGCCCCCTCTTCGAGCTCCTTGGCGATGCCCAGCAAGGA GTCATCGCCGCCGAGCTTGGCCAGGATCTTGTCGGCCTGTTCCTTGACGATGCGGGCCCGCGGATCGTAGTTCTTGTA GACACGATGACCGAAACCCATCAATTTGACCCCGGCCTCGCGGTTCTTGACCTTGCGTTACAAACTCGCTGACGTCGT CGCCGCTGTCGCGAATGCCCTC

NGTCAAGCCGAGCATGCGCGAGGNAACGACCAACAAGCCATGGTGGTTGGCGCCGTCGAGAGGTCGGCGGTCGCACAACGGGAAGATCGCCTTGAGCGTCGCTCGACCGCCGCCTCGAGTTGGGTCATAACGAAGTAGCTGATGCCGATCATGTCGACGTTTCCGTCGCATCAGCGTGCAGCGACCCACTCGACGAGGTCTCGGTGCCGCCGCGCCAGGGCACCAGGGCACCAGTGACGATTCCAGGCGCCGTCGGG

Clone Rv218

Clone Rv219

Clone Rv21

ATACTCAAGCTTGCTGCAGCTTCCTGTGACTGCTCCCGAAACCTGGGGGTGTGCCTGCTGTGTATGCACGGCATACGG ACATCCTTCCCCTGAGACCCGCGGTCGAACCAGCCACGTGTCCATCATCAGGGGTCAACCCCGGCCAAGGGCGACGGC ACGCCAAGTTCGCCGACCGTTAACCTAGTGCTGTTAGCTTCATTTGCTGCGAGCAAAACAGCTGGTCGGCCGTTAGGA ACTGAATTGAAACTCAACCGATTTGGTGCCGCCCGTAAGTGTCCTGGCTGCCGGTGCGCTGGTGTT

AGCTTGCGCGCGTGGCGATCGCGGTTCAAGGCGCGCTCTTCGAGCACAACGAGCGAAGACAGCTCGGCGACGGAGCC
TTTATCGACATCCGTTCGGGCTGGCTGACCGGCGGCGAAGAACTGCTGGACGCGTTGTTGTCGACGGTGCCGTGGCGA
GCCGAGCGCCGTCAGATGTACGACCGGGTGGTCGATGTGCCGCGGCTGGTGAGTTTTCACGACCTGACCATCGAAGAT
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Clone Rv220

AATACTCAAGCTTGCGCACGACCAGGACGTCGAGTGGCGCTTGCAGTGACTTGGCGACCTCAAAGGCCACCGGTACCC CGCCGCGCGCGAAGCCAAGGACNACNACGGCCTTGCCGGATAGCTGCGCCAGGCGTTGCGCCAACTGGCGTCCAGCGT CGCCACGATCGTCAAAGAGCTTCATCTGCCGAGTGTCGCCATCTCATGGCTCCAAATATGGAATTAGGTCCCTGGG CCGACTGACGACAGTCCCTCAGCGACCGGATTGCGCATCCCGCCTTGTACGCTGCTCCGCAAATCCCGGGCTTGCGTC CGCGGAAGCGAACTCGGCGCGCTACGGTGGCTCACTTCGGCCGTGC

GGTTGGTGCGGTCCACCTTCGCGGCGGCGCGCGATATGCCTTGCTGGTCTTGCTCATTTGATATCCAATCTATGGGT
CGTGGTTACTCAGCGGGCCGAAGCTGGCCCTCCCACGGGTAGGGCCCTATTCGACGGTGATGCCCATCGACCGAGCGG
TACCGGCGATGATCTTGGCCGCAGCGTCGACGTCGTTGGCGTTGAGGTCCGTCTTCTTGGTCTCGCGATTTCGCGGA
CTTGATCCCAGGTGACTTTGGCGACCTTGGTCTTGTGCGGCTCCGCCGAACCCTTCGCCACACCAGCGGCCTTAAGCA
GCAGCTTGGCGGCGGGCGGCGTCTTCAGCGTGAAAGTGAAGCTACGGTCTTCATAAACGGTGATCTCCACCGGGATGA
CGTTGCCGCGCTGGTTCTCCGTCGCGGCGTTGTACGCCTTGCAGAACTCCATGATGTTGACCCGTGCTGACCGAACGC
GGGGCCCACTGGCGGGC

Clone Rv221

ATACTCAAGCTTTTCGACCCGCAAGCCGGCGGTGCCCCTCCTCGTTCCGCTGCCCGGTCTGCTCGATCGGTTCGGGGTCGCCGGCTTCGGGGCCCAATTGCCCGGCTCCTCCTCGGGCCGTTCCACAACCCGCATCGTCGCCGGGCTAGGTTCAAGCCATGCCGGTAAACCCCAGGACGCCAGTGCTGATCGGCTATGGACAGGTCAACCACCGAGGCGACATCGACGCCNAAAAT

CAGTCCATCGAACCCGTCGACCTGATGGCCNCCGCGGCCCGGAAAGCCGCCGAGTCCACCGTGCTCGAAGCGGTGGATTCCATCCGTGTGGTGCACATGCTGTCGGCGCATTACCGGAATTCCCGGGCGTCTCCTCGGC

Clone Rv222

AGCAGCTAGCCGCGCTCGCCGCGCTGGTCGGTGCGTGCATGCTCGCAGCCGGATGCACCAACGTGGTCGACGGGACCGCGTGGCTGCCGACAAATCCGGACCACTGCATCAGGATCCGATACCGGTTTCAGCGCTTTGAAGGGCTGCTTCTCGACTTGAGCCAGATCAATGCCGCGCTGGGTGCGACATCGATGAAGGTGTGGTTCAACGCCAAGGCAATGTGGGACCAAGAGCCAAGGCAATGTGGGCCTATCGACGGTCCAGCACAGGAAAAGGTCTATGCCGGCACCGGGTGGACCGCTATGCGCGGCCAACGGCTGATGACGCTCCAAGAAACGCGACCACTACGCCATTCAAGCGGTCGTCGCTCCCGACCGCCCACAGAAAACGCCACATGATGCCGAAGAATTCTACAGCTCCTCCG

Clone Rv223

Clone Rv224

ATACTCAAGCTTTCGTCAGTTCATGGCGCCAGCAGACCAACAAGAGCATCGGGACATACGGAGTCAACTACCCGGCCAACGGTGATTTCTTGGCCGCCGCTGACGGCGCGAACGACGCCAGCGACCACATTCAGCAAATGGCCAGCGCGTGCCGGG

Clone Rv225

ATACTCAAGCTTCCTTTGACCGAACGCGTCCACCGCACCGTGAGATTGGTGGCGCCATTCGTCGTGGTGTAGCTGCTG TTGGCGGCGTCGCCGTATTGTGCGGGCCCAGCCTTGTGCGGGGGCCGCTTCTACCCACAAGTCGGCACTTCCGCAACCG CCCAGCTCGACCGCGAATTACGGCGGCCGCAACGGCCGCCGGAAGGCGTCACGCAATCGCTTATCCTTTCCAGGTTCC CAAATCCTCCGCTTACTTGGGTCCTTCATCGG

GGCAGCGGCGACAACCGGAACGTCCGCACGGTGCTCAATCACGGGTGCACGGTGTGCATCAGAATGGCGGGGGTTCGT
TGTCGCGGTGAGGCGTTCGGCGAGGAGGTAGTGTCTACCCCTTGCCCGCGGGTTCGTGCGGACTGAAAGGGATTTCAT
TGGGAACCCACGGCTGCGTATCGCAGGGCCTCGGTGACGTCTGCTTCCTCNAGCTCAGGAAGTTCGGCGAGAATCTCG
GTGGATGTTATTTGGTCCGCCTAC

Clone Rv226

ATACTCAAGCTTTCTCGGCTTCTCTGATAGCCTGAGAAGAAACCCCAAGTTAATCCGCTGCTTCACCTATTCTCCAGC GCCGGGTTATTTTCCTCGCTTCCGGGCTGTCATCATTAAACTGTGCAATGGCGATAGCCTTCGTCATTTCATGACCAG CGTTTATGCACTGGTTAAGTGTTTCCATGAGTTTCATTCTGAACATCCTTTATTCATTGTTTTTGCGTT

Clone Rv227

Clone Rv228

Clone Rv229

TCCGTACGGCCCGGGTACGCTTCGGTCGCAGTGTGCGAGTGATAGATGACGACCGGGACCTCGTCGGCATCTTCCATA GCCCGCCACACCTTCAGTTGCTCACCGGAATCCAACCGGTAGAAGGTCGGCGAGCGCTCGGCATTGGTCATCGGGATA TGCCGCTCGGGACGGTCAGAGCCCTCGGGTCCGGCCAGCACTCCGCAGGCTTCGTCGGGGTGGTCGCGACGCGCATGG GCCACCATCCATCCACCAGGTCTGCGCGAATCACCCGC

Clone Rv22

GCCTGGCCCAGGTGAAGGCCGACCTCGACGCCAAAGCCGCTGATCCGGCACATGAGTCGGTGGACTTGAAGT
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CGGGGTTGGCCGATCTGGCCCAGGGCCTGGCTAATTGGAAAGCTGGCAAGAACGGGACCCGCAAAGGCCGCGGGTGG
GCTTCCCGCGATTCAAATCCGGGCGGCGTGATCCTGGCAGGGTGCGGTCACCACCGCCACCACGCCCACTCG
ACCGGCGCACGATCACGGTCCCGGTGATCGGGCCGCTGCGGGCCAAGGAACACCCGCCGGGTGCAACGCCACCTCG
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Clone Rv230

Clone Rv231

Clone Rv232

Clone Rv233

Clone Rv234

CGCGTTGAACTGAAGGGGTGCCGCCCGGCTCGAGCAGGCAAGCCATTTGTTCGATGCGGTTACCGAAGATCTCTTCGG TGACTGCCCGCCGCCGGCCAGCTCGGCTCAGTGTCCGGCGTTGGTCGCCGCGGCGACAATCTTGGCGTCCACGGTGGT CGGGGTCATGCCCGCGAGCAGGATTGGCGAGCGGCGGTCAGCCGGGTGAACTTCGTCAAGAGCTGACGCTGCGGTTG GGGAGGCGAATCATGGTCGGTGCGTAGCCTCGACTAGGCCCGGG

TGACAACGCGGCGGCGATTACCCCGCTACCGCAGCAGCATGACGCGGTAGCGAACACCGCCGGATGCAGCGCAGGTGC
GTCGATGTGCTCACGGAATCGCCCCGGCACCCGATCTCGAGGATCACCAGTGCCACCCCCTGCAGCGCGACACCGAC
GATTCCGTACACCGCCACGCCGATCAGGCCCTGGGCCAGCTGATTGGAGCTGGCGTATATGGCGGCGATGGTGACGAT
GGTCATCGCCTCTTACATTGTGGCGGCCAGAACCACGGCGTTGGGGCGGCGGTCGATGAACACTAGGCGACCANATCC
CCGGGGTCAACAGGTTGACCATCC

Clone Rv235

CGCGGACATCCCGAACGAGGACACGCGACCGCTTCGGTGTGTGATCTATCAGGGCTCGCACCACGCGCAACCGCTTCCGGCTACCTAGACGCGGT

GCATGCGGGTGATGCCGTTCTCAGTGCGCAACAGCGTTCGACGCGGCATACCCAGCCGCACATGCCGTGCACGCCGGN GCCGGGGCGGGAATCT

Clone Rv237

:::::::::Rv237SP6.seq:::::::::::

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AGTCGAANGTCAGTCCGGTCTCCTCTCCGACTACGGCCAAGAACTGGGGCGACGGTGTCAGTGCAGAACAGCGGAAAC TGGTGGCGCCCTAGGCGAGCGAACGCTCACAAACGGCGGTGACCGCTTCTGGTCGTGCACCATCGAGCCGTGCCCAGC CCGGCCGCGTGCCGTCAGCCGCATCCACTGGATGCCCTTCTCGGCGGTTTCAATCANGTACAGGCGACGTTCGCCACC ATCGTGCCGGGCACGTTAGCGAGAAACGCCGACTTCACCGATTGCCTCGGTGATGxxxxx

### Clone Rv23

### 

AGCTTCGCGGCGTGGCGATCGCGGTTCAAGGCGCGCTCTTCGAGCACAACGAGCCAAGACAGCCTCGGCGACGGAGCCT
TTATCGACATCCGTTCGGGCTGGCTGACCGGCGCGAAGAACTGCTGGACGCGTTGTTGTCGACGGTGCCGTGGCGAG
CCGAGCGCCGTCAGATGTNCGACCGGGTGGTCGATGTGCCGCGGCTGGTGAGTTTTCACGACCTGACCATCGAAGATC
CGCCGCATCCGCAGCTGGCGGATGCGCCGGCGGCTCAACGACATCTACGGCGGCGAACTGGCGAGCCCTTCACCA
CCGCCGGGCTGTGCTACTACCGCGACGGCTCTGACAGCGTCGCCTGGCATGGCGACCATTGGTCGCGGCAGCACTG
AGGACACTATGGTGGCGATCGTCAGCCTCGGCGCCACCCGCGTCTTCGCGCTGCGCCGCGTGG

### Clone Rv240

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CTGGTCATGGACGTTGCTCCGGTAGTGGCTCACTGCCGATCCTCCTCGTTGAGAGTGCCACCTCAGGGTTGGGTAGGG TTGGGTACTCGAAACCAAGTTACCCACCAGTAACACCGTCAAAATATATCCGTTGCATAGGTCAATGCAAGTTGATGT GAGCTACATTGCACCAACTAACCAACCGGTTGGGTTAGCGGTGATCCTGGCCGTGTCGGTCCTCTCACCTGCGG TGATAGCGATCAAATGAAGAATATGCGGAGTCTAGGGCGGCAGCGCCTGGCANCGTAGATCATCGGCTCACGCGGATG CGGCCTCTTGGTACGGACATGCGCGCG

# Clone Rv241

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### Clone Rv243

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AGGACCGTCAGCACGGCGACGTGCTACTCGCCGAGCAGTGGGAATCGCTCTGCAGCAAACCATTACTCTGCGCGACGT TCGAGATGACCTTCTGAATGGACGGATCTACCTGCCGCGCGACGACCTGGACCGCGTATGCGTCCGCCTCGCCTGGA CGACACCGGGGCACTCTATGACCCCGACGGACGGCTCGCGGTACTGCTGCGGTTCACCGCCGACGCCCGCACGGTACG CGTCGGGACTGCGCTGAGTCCANCCTCGACGCCGTAGCGCTGCTGCTGCGCCATGTCTGGCATCTACCGCCGTCG

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er mate it er tage it also asto auto tage tage that tage

Clone Rv244 CACACGGACGGCGGTGCGGACGCAGCTGACGCGCATGGTGGTCAGCATCGCGGCCGGTCTGCTGTTGTATGCCTACTT CGCGCCGCGCAAATGCTGGTGGGCGGCGGTGGTGGCGCTCGCATGGCTGGGCTGGGTGCTGACCCAACTCTCGAACCA CACCGCTGGGTGGGCTGGGCTATGGCCTGCCATATCGGCCTGGTGTTCTACN  ${\tt CCGATATCCGAGCCGATAGCTGGCGGGGCTCGGGTGGTNGCCAGCGGCGCTGCGACGAAAGTGTGACCGTCATGAAACA}$ GACACCACCGGCGGCCGTCGCCGTCACCTGCTCGAGATCTCAGCATCCGCAGCCGGTGTGATCGCGCTTTCGGC GTGTAGTGGGTCGCCCGAGCCCGGCAAACGCCGGCCCGACACACCCCGGAACAGGAAGTCCGGTCACCGCGCC Clone Rv245 GCTTCAGGACAAATTGNATCCCTATGCACCCGTTGTCACGCCGATGAGTGAAGACTGCACGCAATCGCCGGAATCCGG CAAAACCCTGCACAAGCGAAATCAACCGGAGGCTGACAAGGCAACGTCGGTGATCCGTACCGCCTGGTTGGACAAACG GCAGAAGGCGCCTCGTCCGGTCCATCTACGCCGAGCACACTGGTGATAGCGCCATCGGCATCGGTGCGGCCACGGTGG AGACGAACGTCCGCNGGCGTCTGGGTCAGTAACCCGCCGACCAGTTCTCGGGCCAAGCTGGTCAACATCGGĠCGCCACG TCTCCAAC

Clone Rv249
::::::::::Rv249SP6.seq:::::::::
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AACTTCATCCGTTTCATGTACAACATTTTTAGAANCATGCTTC

TCCGTACTGGTCGGGTACGCTTCGGTCGCAGTGTGCGAGTGATAGATGACGACCGGGACCTCGTCGGCATCTTCCATA GCCCGCCACACCTTCAGTTGCTCACCGGAATCCAACCGGTAGAAGGTCGGCGAGCGCTCGGCATTGGTCATCGGGATA TGCCGCTCGGGACGGTCAGAACCTCGGGTCCG

Clone Rv251

::::::::::Rv251SP6.seq::::::::::::

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CG

GGGTGTGCCTGCTGTGTATGCACGGCATACGGACATCCTTCCCCTGAAGACCCGCGGTCGAACAGCCACGTGTCCATC
ATCANGGGGTCAACCCCGGCCAAGGGCGACGCCAAGTTCGCCGACCGTTAACCTAGTGCTGTTAGCTTCATTT
GCTGCGAGCAAAACAGCTGGTCGGNCGTTAGGAATGAATTGAAACTCAACCGATTTGGTGCCGCCGTAGGTGTCCTGG
CTG

Clone Rv252

Clone Rv253

:::::::::Rv253T7.seq:::::::::::

GCTCAAAGGCACTACTGGCACCAAGGCCCACACGTCACCTGTGACTCCTGCGCCGACCCGCCGAGGTCTGGCCGTTACCCGAACGGCCGAGCCGGGAGTTGGTACCATCGAACAAGACAAGGTGCATGGGCGGAGTTGTTCCGCCACTTCGTCGATGACGGGTC

Clone Rv254

CGATACCGGCTGCTTACCGAGACATCCACCATGCCACCCGAATCACCGCACGCGCGCAAATCGCACAACAGCTTGACG CCTTGCAGGTTCCGCGATTGGAATTGCCGACGGTCTCTGACGGCGTCGACCTTGGCAGCCTCTACGAGCTCTCGGAAT CACTTGCCCAGCAGGGGGTTCGATGAGTGTCACACCGAAGACCTCGATATGGGCGCAATCCTGGCCGACACATCCAAC CGGGTGGTTGTGTGCTGCGGCGCCGGTGGGGTCNGCAANACACTACCGCGGCCGCGCTGGCGTTGCGCGGCCGAAT ATGGCCGCACTGTGGTCG

Clone Rv255

:::::::::Rv255SP6.seq:::::::::::

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Clone Rv257

CTATCGTACCCGCGCCGGTCACCTTCTGGATATCGCCGGCCTGGTCAAGGGGGCGTCCGAGGGAGCCGGGCTGGGTNA
CAAGTTCCTGGCTCATATCCGCGAATGCGACGCCATTTGTCAGGTGGTGCGGGTGTTCGTCGACGACGACGACGTGACTCA
TGTCACCGGACGGGTCGATCCCCAGTCCGACATTGAGGTCGTCGAGACCGAGCTGATCCTGGCAGATCTGCAAACCCT
GGAGCGGGCCACGGGCCGGCTGGAGAATGAAGCGCGCACCAACAAGGCGCGCAAGCCGGTCTACGAAGCGGCACTGCG
TGCCCAGCANGTGCTCGACGCCGGGCAAGACGCTGTTCGCCGCGGGGGTGGATGCCGCGCGTTGCGCGACTGAAACT
GCTGACCACCAAGCCCTTCCTGT

Clone Rv258

:::::::::Rv258T7.seq:::::::::::

Clone Rv259

::::::::::Rv259SP6.seq:::::::::::

Clone Rv25

::::::::::Rv25SP6.seq:::::::::::

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CAGGCATGCAAGCTTGCGATGTATCAACACGCCGTTGCGCAGCGTGAGCCGATAGTTGACATCCGGCTCGGTGAAGGT
GAAATCGATGGCCAGGTCGAGGTCCCATGCGCGTGGGCCATTGATGCTCGATGGCCAGGACGTCAAAGATTTGGTCCG
CGTCAGCTGGGCGAAAAACGTGGGCGCCGGGACTTGCCCGGAGCTGCCCGGGGTTCCCGTCGCGCAGCTCGGCGCCCC
GGTCAGAAAGAAATTGCGCCAGGTCGCACACTCCGCGCCGTAGGCCAGCTGCTCCACGGTGTCGGCATATAGCCCGC
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CTTCGCCGGGCCACTCCAGCACTCCGTC

#### Clone Rv260

ATACTCAÃGCTTGACCGACGCTGATCGCACCGCACGCGGGÃÃCCTCAÃĞGGCÃCTACTGGCACAAGGGCCCACACGTC
AACCTGTTAACTCCTGCGCCGACCCCGGCCGAAGTCCTTGGCGTTAACACCGAACGGGCCAACCCGGGAATTTGGGTT
CCATCAAAACAAATAGCAGGTGCCTGGGCGGAGTGTTC

GTCGTCGTGTGCTGGGGCGTCCGTATCAGCACGCCCACGAAATGGGGCACAAGAAGGATTCCTGGAACGGTGGCTGTCCAAGATCACCCTCGCCCAAAACTGCTACGGGCACTTCTACATCGAGCACAACCGTGGCCATCACGTCCGCGGTGTCCACACCGGGAGG

### Clone Rv261

ATATGCCTTGCTGAGCTTTTCGGATCGCAGCGAGTCGTACCCGCGCCGGTCACCTTCGTGGATATCGCCGGCCTGGTC
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GTGCGGGTGTTCGTCGACAACGACGTGACTCATGTCACCGGACGGGTCGATCCCCAGTCCGACATTGAGGTCGTCGAG
ACCGAGCTGATCCTGGCAGATCTGCAAGCCCTGGAGCGGGCCCACGGGGCGGCTNGAA

GACACCCTGGTCACGGGTGAGCAGGACTCGATTTCTTCGCTATTGGTCGGCGCTGTTGAGGCACAGCACGCCGCTGAG GCCGTCGCGTCCTCGCTGTGCTCGGTGGAGCGCGCGCCGCGCGGCCGAACATCGTAAATCAAGCGTATTCGTC AACAGATATCATCAATGTCGGCGCTGGACTATTCAAATCATCGATATACTGGTGACCTGGTCCTTCGCCATCGATCAA TGGCGATAGTCACGCAGATCGTCACGGACATCGTCTGCGCCCAGCTGGCCCGAACAGATGCTGCAACCCATCG GGGTGGTATCNCCGCGGTGCTCGGCGATGGTCCAACAATTCTTGCGGTCCAAGCCCGAAACCATCCGGCCATGAGTTC ACCGGCATGGCGCAACGGCTGGTGCCGGGCAAAACGCGGCGCGATCGAATTC

## Clone Rv262

TGTAGAAGGTGGGTCCCGTCCAACTTCGCGGCGGCGGCGGCGATATGCCTTGCTGGTCTTGCTCATTTGATATCCAATC TATGGGTCGTGGTTACTCAACGGGCCGAAGCTGGCCCTCCCACGGGTAGGGTCCTATTCGACGGTGATGTCC

CCCGAATCCGGTGGCCGGCAGGGGGCCTGGCGACGTGGACACCTTCTAACTTGTCTTTACCGGTCACTGTTGCACCCC
AACACCTTTAACGACGTGGACGGACGTTACATCGGATTCGACGGTGTCATCCACAGCGTTGCCATTGGGCACACCCAC
TACGCCAATTTCTCCGACTGGGACACCTACCGCAGCCTCGCCCCACTGCAGGGACTGTTGTTCCCGCAACGGGCCATC
GACATGATCCAGTCGTTGGTGACCGACGCGGAGCAGACTGGTGCGTATCCGCGTTGGGCGCAAATTCCGCCAC
CGGCATGAT

### Clone Rv263

 ${\tt TTGAGATGCTGGGGATGCCGATGGTTGGAACATGGTCCCCTGGCGTCGAATACGCGCGAGCGCATGAGCTCACCGGTCGGAACAACGTATCGAAGAACTCGCACTGCTGGCAGATGGTATCTCCGATGTGGTTGTAATTTGTATCCCAACTCTAACTGTGCTATCGGATCTGCGTGAATA$ 

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Clone Rv264

CAAGCTTAAGCTGGTTCCGGCCACTCCATGAGCCGTAGTGCAATGGTTCGTGCACGGCGAGGCCGAACTTGCCATAAA CATCCCTGACGAAAGTCTCCGGCAAGCCGATTGCTTCTTCGGGCCGCTTCTTGTGGATTGTCCGATAACCCGGTCCCT CATGCTGGAAGTTGTGCGCACTCTTTCCTTCCGCGATGTGGGCTAACGACTCGTCATTGAGCAAGAAGTACGTGCACA GGCATCGTCCGCCGGGGCTTCAGCACGCGGGAGATCTCGTCCAGATAGTGCTCCACGTCCGGNGGGAAACATGTGGGTG AACACCGAGGTNAGAAACACCNCATCCAACGACGCATCCGGGATATGGAAAGCGAAA

Clone Rv265

GCTTAGCGGTCTTGCTCGAACCGACATTGCGTGCCACTCATGAGCGGGTGGCGGTCGCGGTGCTTACACATCT

Clone Rv266

:::::::::::Rv266SP6.seq::::::::::::

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GCTCTCAGCGCACGTTCGGCGCCGAGGNGGCTAGTCCCTGGTTAAGCAATGTCTCGGTCGCCGCAGCAGCGCGCATG
TCGCCAACCCGTCNACCGCGTTGCGCATGTCCGGTACCGACGGAAACGACGGCGCGATCCGGATGTTCTTGTCGTCCG
GATCCTTTCGATACGGGAACGACCCCCCGCCTCGGTCACCGCGATACCAACGTCCTTAGCCAANGCTACNGTCCGGCG
CGCGGTCCCGGGCAACACGTCGAAGCTGATGAANTAACCACCCTTGGGCTCCAAGANGCGATCTTGGACTCCTT
AACCGCTGATNCAA

Clone Rv267

GGCCGAGTCCAGCACTTCGCACTATGTGCAGACCAAANACCCGGTGGTCGCCGCGCTGCGGCAGCGGCTGGCAACGGC GCCGGTGATCACCGAGTGGTGCGAAGTTGCCGACCGGCAGTTCGCCGCGGGCTTACTACGAGAAGGGCCTGCGCGACG TCATCAGGTATCACGTGTCGATGACGTCGAGCGTTAACTTCCCCGACCAGACGGCGACCTCGCCGATGGACCCCGCGT TGTACCTGGTGTGGGCGCAAGCTAACGCCGCCGCANGCTATCGGTACTCGGTCGAAGCGCAGCCGGGGTCGCAAGCGC TAGCGGGCAAGGTCGCGACGATCTCGGTCACCTGGACCAACTACGGCGCTGCTGCCGCCACCGAATAGTGNGTGCCCG GCTACCGGCTGGTGGATTCCACGGGACATGTGGTTCGGACCTGCCGGCAGCGGTGGAACTGAAGANGCTGGTCT

Clone Rv268

AGCTTCAAGGACATCGTCATCGCGACCAAAACCGCGAGCTAGGTCGGCATCCGGGAAGCATCGCGACACCGTGGCGCC GAGCGCCGCTGCCGGCAGGCCGATTAGGCGGGCAGATTAGCCCGCCGGGGCTCCCGGCTCCGATTACGGCGCCCCGAA TGGCGTCACCGGCTGGTAACCACGCTTGCGCGCCTGGGCGGCGGCCTGCCGGATCAGGTGGTATATGCCGACAAAGCC TGCGTGATCGGTCATCACCAACGGTGACAGCAGCCGGTTGTGCACCATCGCNAACGCCACCCCGGTCTCCGGGTCTGT CAN

Clone Rv269

AGCTTGTCGATCGTCCGGCAGCGTCCGGCGAGTCAAGTCGAAGCCAGTCCGGTCTCCTCTCCGACTACGGCCAAGAAC
TGGGCGACGGTGTCAGTGCATACCAGCGGANACTGGTGGCGCCCTAGGCGAGCGACCGCCTCACAAACGGCGGTGACC
GCGTTCTGGTCGTGCACCATCGAGCCGTGCCCATCCCGGCCGCGTGCCGTCAGCCGCATCCACTGGATGCCCTTCTCG
GCGGTTTCAATCAGGTACAGGCGACGTTCGCCANCATCGTGCCGGGGCANGG

TTGGTGATCATCGNCCCAACGACCCCGAGGCGATGTTCTTGCACACCGAGGAGTGTCGCAAGCTGGGGCTGGCCTTCGCCGCCGATCCGTCTCAGCAGCTGGCGAAGCTGTCGGGGTGAGGAAATTCGCAGGCTCGTCAACGGTGCTGCTTACTTGTTCACCAACGACTACTAATGGGATCTGCTGCTGTCCAAGACCGGCTGGTCAGANGCCGATGTGATGGCGCAGATCGACCTGGCGGTGACCACCATTGGGTCCTAAGGGTGTCGATTTGGTAGAACCTGACGCACCATCCACGTCGGCGTTGGTCCCGAAACAGCCAGACCGA

Clone Rv26

:::::::::Rv26SP6.seq:::::::::::

GGCTCGTATGTTGTGTGGAATTGTGAGCGGATAACAATTTCACACAGGAAACAGCTATGACCATGATTACGCCAAGCT
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TGGTTATCGTGGGTACCGTCGTGCTTTCCATGGGCGCCTCTTTCGGGCTTTCCGTATTGGTCTGGCAGGACATTCTGG
GTATCGAGTTGTACTGGATGGTGTTGGCGATGTCGGTGATCCTGCTCCTGGCGGTGGGATCCGACTACAATCTGCTGC
TGATTTCCCGGTTGAAAGAGGAAATTGGGGCCGGATTGAACACCCGGAATTATCCGTGCCATGGCTGGTACCGGGGGAG
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::::::::::Rv26T7.seq::::::::::::::

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Clone Rv271

CTCAAGCTTGGAGGCGTGGCGATCGCGGTCCAAGGCGCGCTCTCCGAGCACAACGAGCGAAGACNGCTCGGCGACGGA GCCTTTATCGACNTCCGTTCGGGCTGACGGCGGCNAAATAATGCTGGACTCGTTGTTGTCGACGGTGCCGTGGC GAGCCGAGCGCCGTCAGATGTACGACCGGGTGGTCTATGTGCCGCGGTTGGTGAGTTTCCACGACCTGACCATCGAAG ATCCGCCGCATCCGCTGCTGGCGCGGATGCGCCGGTGGCTCAACTAATTCTACGGCGGCGAACTGGGTNATCCCTTCN CCACCGTCGG

Clone Rv272

AGCTTGGCGTGACACCAACACGGGCACTTAAGATGGCAATGCGCCGCCTACCTGCACGTTTTCGCGATGTCAGAGGA
TGCCGAGGGGAGAACAATGCGAGCACGGCCGCTGACGTTGCTCACCGCTTTTGGCGGCGGTGACATTGGTGGTGGTTGC
GGGCTGCGAGGCCCGAGTCTAGGCCGAAGCATATAGCGCGGCCGACCGCATTTCGTCTCGACCGCAAGCGCAACCTCA
GCCGCAGCCGGTGGAGCTACTGCTGCGCGCCCATCACGCCCCTAGGGCTCCGGCGGCGTCGCCGAACGTCGGGTTTGG
CGAACTGCCTACCCGGGTCCGGCAGCAACCGAT

Clone Rv273

GGGTCGACTTTCTGCAAGGCGAGGCTACACCGTCGTCGTCGTGGTATGCGATAGCCATCCCGTCGGGCTACTCGCCATCACCGATCAGCTTCGCCCACCGATCAGCTTCGCCCGAAGCCGCCGTGTGATTTCCGCTGCGACCAAACTGAACGGGGCCAAACCGGTATTGCTTACCGGCGACAACCGGGCCACCGCCGATCGGCTCGGTGTTCAGGTTGGCAT

AATCCGAAATCCTGACCGATACTTGAACCTGGTCTCGTTCGGCAATAACTCGTCGGCGTGCAGGACGCGGCGCAAACG TACTTCGGCATCAACGCGTCCGACCTGAATTGGCAGCAAGCGGCGCTGCTGGCCGGCATGGTGCAATCTAACAGCACG CTCTTCCCGTACACCAACCCCGACGGCGCGCTGGCCCGGGCGGAACGTGGTCCTCGACACCATGATCGAAAAACCTTC CCGGGGAGGCGGATGC

Clone Rv274

TTCCGAATTTCGGGTCCNGGTCATATGACCCTCATGGAAGAAGAAGAGCGCCCCCCCGCGCCCGTGCGACGGCGAATGAAACCCTCACCCAGGCCGATTGAACGCCGACAAGACGGTGGAGCAGGTCGAAGACGTCCTGGACGGTCTGGGTAAGA

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#### Clone Rv275

TCATCCCGACCAAAACGCGAGCTAGGTCGGCATCCGGGAAGCATCGCGACACCGTGGCGCCGAGCGCGCTGCCGGCAGGCGCAGTATTATCCCGCCGCGGCTCCCGGCTCCGAGTACGGCGCCCCGAATGGCGTCACCGGCTGGTAACCGCTCTTGCGCGCCTGGGCGGCGCCTGCCGGATCAGGTGATCACCCCAACGGTGACAGCCGGCTGTGTGCACCAACCGATCGACCGCCCCAACGGTGACAGCCGGTTGTGCACCAACCGATCGACCGCCCCAAGCCCACATGAACAAACCCCGGCATCACCGCCCCAAGCCCACATGAACAAACCCCGGCATCACCGTTGCCGATCGGCATCGCCACATGAACAAACCCCGGCATCACGTTGCCGATCGGCATACCGTGA

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TTGGCGGGTTGGCCCAGCAGCCCGCCGGTGACGGCGACGATGCTGGGCTGGTTGCGGCCCTGCGCCACCGCGGCTTGC
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CCGCGCGGCTCGACGAGTTTTTGGCCTGGACTACCCGCGTGGCCAATCTGCTGAACTCGCGGCCGTGGTGGCCTGGA
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AGCCGGTCCGGTTGCCACGCAAAGGCCATGTCTTCGTCGGTCCGACCATCGGTACCGGGACACGGCGCTGTATTGCCC
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ATGATCGTGTTGGTCTCCCT

### Clone Rv276

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CGAACTGAGCCCATAGAAAGGCAGCGACTAATTCGCTGGGCAAATAGGAAGACCCTTTGTCCTGCCACGTATATTTGT
CGACCTCGTTGCGAAGGAAGCGGCTGCGATTGGTGCCCTTTTCCCTGGAGAATCTCTTGCCCGGAGCAGGAAGTCTTAT
GAGTTGACAAGCAGGGGCGCCGCCTTCGCCGGAAATCACATTCTTGGTCTCGTGAAATGAGAGCGCTCCCAGGTCGCC
GATGCTGCCGAGCGCCCCCCCCACGATACGACGCCATCGCGCCTTTGGGCCGCGTCTTCGACCACCGCCAGGTTGTGGTG
CGTGGCGATCTTCATGATCGCGTCCATCTCGCAGGCCACCCGCATAGTGAACGGGGACCATGGCCTCGGTTCGCGG
TGAA

## Clone Rv277

 ${\tt CTTAGACGCCACCTCCGGGCCGAGCTCCACGGGGTGGATAAGTACGGCCGGATGTGGCCGCAATGGGAAGTTGTTGCCCGGCTTGACTCCGGGTTAACGCCGGATTCCACCACATCCCCTTGCGAAAGGCCGTTGGGTT}$ 

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Clone Rv278

AGCTTACGCCGCTTCGGATTTGGGACGCCGCATCGAAAGCGCAGTTGGAAGCGCGGCGCCCGGCTGGTCGAGCTCGAGCAGCCGCAATCCCAGCCCATGCCCGTTGAGGAGCAAGTGGTTTCGATCTTCCTGGGCACCGGCGGTCACCTGGACTCGGTGCCCGTCAAGGATGTCGGCGGTTCGAAACCGAATTACTGGACCACATGCGGGC

CGACGGGACCTCGTCGCATCTTCCATAGCCCGCCACACCTTCAGTTGCTCACCGGAATCCAACCGGTATAAGGTCGGC
GAAGCGCTCGGCATTGGTCATCGGGATATGCCGCTCGGGACGGTCAGATGCCCTCGGGTCCNGCCAGCACTCCTCAGG
CTTCGTCGGGGTGGTCGCGCACCGCATGGGCCACATCGCATTCACCAGGTCTGCGCGAATCACCAGCACGTANACGGTT
CCTTTCCTAAGCAACACCGAAATTTCAGGACCCGAATGCTCCGGGAAAACATGTCACGGTAAGTCCGGTATTCCGGGT
ACCGGTTGAGCATTGA

Clone Rv279

CGGCATCGGTTTGGGCTGTCACCAGCAGTTGGTAGTTCTTCACTACTGTTGTTCGAGCGTCGAGCCGCCGCGCGTGTC
GAGGTCGCCGGACGCCGCCAGGCCGGTCAGGGTGCCCTTCCAGTCCACGCNGCTGTGGTCGGCTAACCGCTTA
TCTTCAATCGAGACNATCGCCAGCTTCATCGTGTTGGCGATCTTGTCCGAGGGCACCTCGAACCGCGCTGCGANTAC
AGCCACGCGATCGTGTTGCCCTTCGCGTCGACCATCGTCGATACCGCAGGCACTTGCCCCTCGAGCAGCTGGGCCGAT
CCGTTGGCAACGACCTCAGAGGCACGATTGGACATCAGCCCTAGCCCGCCTGCG

:::::::::::Rv279T7.seq::::::::::::

Clone Rv27

::::::::::Rv27SP6.seq:::::::::::

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GGCGCCGACNATGGCGCCTGGACCGATCTTGTGCCGCTTGCCGACGGNGACGCGGTANGTGGTCAAGTCCGGTCTACN
CTTGGGCCTTTGCGGACGGTCCCGACGCTGGTCGCGGTTGCGCCGGAAAGCGGCGGGTCGGGTGCCATCAGGAATG
CCTCACCGCCGCGGCACTGNACGGCCAGTGCCGCGGGATGTCNGCCATCGGGACATCATGCTCGCGTTCATACTCCT
CGACC

Clone Rv280

CCGGCGGAACTCAGACGTGCTGGTGCGGGCATGGCACCGCGGGCAAAGCGCACTTCTCCGGGGACGACAGCAA GCGACCGCTAGACAAGAGGGGTCGTGCGCAGGAGGCATGGTACCACAGCTGCTGGCGTTCGGCGCCACCGATGT TTATGCCGCCGACCGGGTGCGCTGCCACCAGACGATGGAGCCACTCGCCGCGGAACTGAACGTGACCATACACAACGA GCCCACCCTGACCGAAGAGTCCTACGCCAACAACCCCAAACGCGGCCGACACCGAGTGCTGCAGATCGTCGAGCAAGT

 ${\tt AGGCACCCGTGATCTGCACGCAGGGCAAGGTCATTCCCGATCTGATCACGTGGTGCGAGCGCGACCGTGTGCCCCGACAGTCCCGCAATCGCAAAGGCAGCACGTTGGTGT}$ 

### Clone Rv281

### Clone Rv282

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TGCACCCAACTTACTGAGCATGCTAACGCTGGTCGTGCGGGGTCTTGTTCCCGCGTGTCGGCAGGGCACACGCTCGGGGCGTAGCTGGGAGAGGCCCCGGTCAAGCCCGGAGAGCACTCCAGTCCGCCAGCTTGACCGACTTTCGATGAGAACGCGCTTCTCGCCGTATTGAACTGGCGTGCTGACGGTCGCTGAGCAGCGCTCGCCGAGTGCGGCCGCTGATTCTTTCATCGAGCAGACGCGCATTCGTGTTCGGCCGCCGCTGATTCTTCATCGAGCAGACGCGCATTCGTGTTCGGCCGC

### Clone Rv283

AGCTTACGGCCGGTCGACGCGACGAGTGGTTCATGACACCCACAAACCGTCAACGCCTACTACAACCCGGGGATGAACG
AAATCGTCTTCCCGCAGCGATTTTACAGCCACCATTTTTCGATCCGCAGGCCGACGAGGCCGCCAACTACGGCGGGAT
CGGGGCGCGTGATCGGGCACGATGATCGGGCACGGTTTCGACGATAGGGCGCCCAAATACGANGGCGACGCAATCTGGT
CNATTGGTGGATCGA

ATGTCGTCACGTCACCACAATCGCGAGGACCCAATCATGCCGCCCAGGGCCGCCAACCCAATGGTGGCCGCGAAGCGGCAGCTCGATCGCAGCGGCGGGGGGCGCGCGAGCGGCCGCCGAGTTGATTCACGAACAGGGTGAGGTCATAGGCGGGCAGGATAGTGACGAACGCAAGACCTATATCTGCCGTCGGAGTAAGAATCGAGTAGCCGGTCGACCAACGGAAGCGAAAGTGTCCGCGATTGATGAGCGTCGCCGGTTGTGGCGGCGGTGGC

### Clone Rv284

CTGCCGCGGTGGCGGTCAGCGCCTGGCAAGTCACCGCACCGCCGTCCGGTTCATCGGCAGGCTCCCCCGAAAAGGGCC
CTGGCAACAGAAGGTGATCAATGAGCTCCCGCAGACCTTCGCCGATCTGGGACCGACATACGTGAAGTTCGGCCAGAT
CATCGCGTCCAGCCCGGGAGCATTCGGTGAGTCGCTGTCGCGGGAATTCCGCGGCCTGCTCGACCGGGTGCCGCCCG
CAAAAACCGACGAGGTGCACAAGCTCTTCGTCGAGGAACTCGGCGACGAGCCGGCCCGGCTGTTCGCCTCCTTCGAGG
AAGAACCGTTCGCGTCCATCGCCCAAGTGCACTACGCGACCTGCGCAGCGGCGAAGAAGTGTGGTCAAGATC
CACGGCCGGGCATCCGCCGCCGCTTT

## Clone Rv286

::::::::::Rv286SP6.seq:::::::::::

:::::::::::::::Rv286T7.seq::::::::::::

TCAGGACGCTTATGGTTGGCAGATGGTCGCCCTGGCGTCGAATACGCGCGAGCGCATGAGCTCACCGGTTCGGAACAA CGTATCGAAGAACGTCGCACTGCTGGCAGATGGTATCTCCGATGTGGTTGTAATTTGTATCCCAACTCTAACTGTGCT ATCGGATCAGCGTGAATATCGAGATATTGCGAATGCGATGACAGGCCGCCATTCGGTTTATTCGCTTACGCTTCCCGG GTTCGATTCGTCTGATGCACTGCCGCAAAACGCGGATATGATTGTTGAAACCGTATCTAACGCAATTATTGATGTGGT AGGCGGCAGCTGCCGTTTTTGTGCTGTCCGGCTATTCATCGGGTTGGGGGGTGTTTTGGCCTCTCCCAT

Clone Rv287

::::::::::Rv287T7.seq::::::::::::

Clone Rv288

Clone Rv289

Clone Rv28

:::::::::::::Rv28SP6.seq::::::::::::

Clone Rv290

GCGCGCCATGTTGAGGTTGTCCGACGGTGACGACGGTGAACCACAACTGTTTGACCTGTCCGCACACACCGTGTGGAT
CGGCGAGCGGACCCGACAAATCGATGGCGCGCACATCGCGTTTGCCCAGGTGATTGCTAATCCGGTCGGGGTCAAGTT
GGGCCCCAACATGACCCCGGAACTGGCCGTGGAGTACGTCGAGCGGCTCGACCCGCACAATAAGCCGGGCCGGCTGAC
TTGGTGAGCAGGATGGGCAACCACAAGGTCCGCGATCTGTTGCCACCGATCGTGGAGAACGTCCATGCCACCGGGCAT
CAGGTCATCTGGC

Clone Rv291

::::::::::Rv291T7.seq::::::::::

CGACGCTGGGCCCAACTGCGACCÁCCAGGTCCTGGTATGGCAGGACATGGCCGGGTTCAGCGGCGCCAATACCG

Clone Rv292

TAACGACTCGGGTCCAGCGACCGCCCAACACNAACGGCCGGACNACGTGGGCCAGGGTCGCGGCCTCCCCTACAAAC AGGATCCGTTGCCTGCGAACGACAGGCTCCGGTGCGGCGTTGGGCGCCGTGCTCCAGCGTCCGGTCCGGGTCC

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CCGGCGACGCTTGTTTCCTCCATACTCGCCCCCTAATCTCGAGGCAGCCCGTACCCGCAGGCAACCTCCCAAAAATGC
AATCCCCCAAAATGCATGCGTCNAGCTATTTCTCACACCGACCGCTAGTTGCGGATCANAAATCCGTTGGGCGCGGA

Clone Rv293

GCTTTTCNGATCGCAGCGAGTCGTACCCGCGCCGGTCACCTTCGTGGATATCGCCGGCCTGGTCAAGGGGGCGTCCGA GGGAGCCGGCCTGGGTAACAAGTTCCTGGCTCATATCCGCGAATGCNACGCCATTTGTCAGGTGGTGCGGGTGTTCGT CAACAACNACTTGACTCATGTCACCGGACGGGTCGATCCCCANTCCGACATTGAGGTCGTCGANACCGAGCTGATCCT GGCANATCTGCAAACCCTGGAGCGGGCCACGGGCCGGCTGGAGAAGGAANCGCGCACCAACAAGGCGCGCAAGCCGGT CTACGACGCGGCACTGCGTGCCCAGCAGGTGCTCGACGCCGGCAANACGCTGTTCGCCGCGGGGGTGGATGCCG

Clone Rv294

GCGAGGCGGTATCGCTTCCCGTCGTACCGGCGACCGCCGAGAAGCTCGTTTTCCCAGTGTTGCTGGGGATTCTC ACGCTGCTGCTGANTGCGTGCCANACCGCTTCCGCTTCGGGTTACAACGAGCCGCGGGGCTACGATCGTGCGACGCTG AANTTGGTGTTCTCCATGGACTTGGGGATGTGCCTGAACCGGTTCACCTACNACTCCAAGCTGGCGCCGTCTCGTCCG CAGGTCGTTGCTTGCGATAGCCGGGAGGCCCGGATCCGCAATGACGGATTCCATGCCAACGCTCCGAGTTGCATGCGG ATCGAATACNAATTGATCACCCA

TGGGTCTTGCCGGCGAGCCCAGCGAAGTCGCTAGCGTGGCCGTGTTTCTTGGCTTCGGATCTATCCTCGTTACATGAC
CGGCACCGTGTTGGACGTGACTGGCGGCCGGTTCATATGACACCGAGATCATTGCCACGGTACGGCAATTCGTCAAGA
AGGAAATCTTTCCCNATGCACCGGCCCTCGAACGTGGCAACAGCTACCCGCAAGAAATCGTCGATCGGCTGGGTGTTA
TTGGCTTGCTCGGTCGCCGGCTGCAAGGGTATCGACCACCACCGAGTTCATTCTCGGGCGTGCCGGCGCATTCGAGCTG
GCGGTGCGCGCTGCCAGCACCGTCATAAGTACTTGANGATGGTCAAACGTCGGACGAACCGCCACCACGTCGCTGCC
GAACGG

Clone Rv295

TCTCCACGGCGTGGATCAAGGTACCGGCCGGGATGTTGCGCAATGGCAGGTTGTTGCCCGGCTTGATGTCTGCGTTAGCGCCGGATTCCACCACATCCCCTTGCGAAAAGTCCGTTGGGTGCAATGATGTAGCGCTTCTCCCCATCGAGATAGTGGAGCAACGCAATCCGTGCGGTACGGTTCGGGTCGTACTCGATGTGCCGGACCTTGGCGTTGACACCATCTTTGTCATTGCGCGAAAAGTCGATCATCCGGTAAGCGCGCCTTATGACCGCCGCCTTTTGTGCCGGGTNGGTAATCCGGCC

WO 99/54487 PCT/IB99/00740

84

Clone Rv296

GCCCGGTTCGATCGGCCATGTCCGCAGTCGTTACCGGAGGCGGTCGTGGCCGCGCTAATCGGCGTCGGCGCCGAC
AAGATGTGGGATATCCGCAATCGGGGCGTCATCCCTGCGGGCGCGCCTCCCCCGCGTCCGAGCCTTCGTCGACGCAATC
GAGGCAAGTCACGACGCGGATGAGGGGCAGCAGTGAATTACAGCGAGGTCGAGCTGTTGAGTCGCGCTCATCAACTGT
TCGCCGGAAACAGTCGGCGACCGGGGTTGGATGCGGGCACCACACCCTACGGGGGATCTGCTGTCTCGGGCTGCCGAC
CTGAATGTNGGTGCGGGCANCGCCGGTATCNACTCCCGTGGAACACACCCGGGGC

::::::::::::::::Rv296T7.seq::::::::::

CTCGGCGTGGATATCGGTGTAGCCGGCGCCGGTGAANGTCGGCTCCTTACGTCCACTCGACAACAGCTCATAGCGATC
CAACCAGTANGCAACCGCCTTCAGCAGTACAACCGCGCGGGGAACACTGCGAGTTGAACGCGAGCTGCCTGGGTCAG
CATGCCTCTGCCGGTTGTCAGCCGAAGGCCGCCGAACAGGTAATGCGTCAACAGGCTCGCTAGAAACGCCAGAACCAC
GGCCACGAACAGCCAGTTCAGCACCGACCGGTAGAACGGCAGATCGAAGACGAAAAAACCCAATGTCATAGCCGAATT
CGGGGTCCACGATGCCAAAGGTGCCCCCGTGTACAACAACTGAACCTTCACCCA

Clone Rv29

Clone Rv2

::::::::::::::Rv2T7.seq::::::::::::

Clone Rv301

Clone Rv302

TACTCAAGCTTGAACGCTGCGAGCGAGCCCATGTAGAGCGTTTGGTACCAAACCGATCGGTGGGCCAACTTGCCATGG
GCTCACAGCGGCTATCGCGAGCGTTAGCCGATCATCGGCCAGGCGACGGTGGCCTGAGCGGCAGGGGTTGCCTTATC
CATCCTCTTGCGGCATGGTTGCCGCAGGGAGTGCCGGTAAGTCTGGTCGGCAACCTGGCCCGCTGCGGGTTGGGTTCG
GATTCCCTCGGCTAGTAAGGTGCTCGCCTGGTGTTACAACGAATCGCTAGACAGCTCTTATCGGGAGTGGCCGTCGCG
ATCGTTGCGCTGCCGCTGCGGATCGCGTTCGGCNTTACCGCCACCGGAACGTCCCAAGGTGCCGCTCATCGGGCTCTAC
GGCGCCATCTTCGCCGGATTCTTCCCNGCCGTGTTCGGTG

GCGGTGTCTGAACTTCGCCCGTTCCCTCCAGCGCATTGAGCTTCAGCCCGACCGGCAGGTAGGGAGTCGGCATGCGGT CCTTCGCCCCGACCCCGCTGGCTAAATAGCCACCCCCGAGCGCGGTCACGGTCTTTGCACCGGGACGACGACGATACCG GCAGCGCGAACATCGCCGCGGGCTGCAGCGTGAACGTCGAATACGAGTCGAACAGTGTCGGCGCGTAAAAACCCGAGC CGGCGGTCGCTTCGGTAATCAACGGCTCCTGCGCAACCAGCTGCAANTCNCCGGTGCCACCGGCGTTGACAATCTTGA TNTCGGCGACCTCGCGCACCAN

Clone Rv303

Clone Rv304

Clone Rv306

CTCGGGTACGCTTCGGTCGCAGTGTGCGAGTGATAGATGACGACCGGGACCTCGTCGGCATCTTCCATAGCCCGCCAC
ACCTTCAGTTGCTCACCGGAATCCAACCGGTANAANGTCGGCGAGCGCTCGGCATTGGTCATCGGGATATGCCGCTCG
GGACGGTCAGAGCCCTCGGGTCCGGCCAGCACTCCGCAGGCTTCGTCGGGGTGGTCGCGACNCGCATGGGCCACCATC
GCATTCACCAGGTCTGCGCG

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Clone Rv307

CTCAAGCTTCAATTCCTCCACGACGCGTTCCCAAATGAATTTCCCGATCCCACAATCTCGGTTCAGATACAGGTCGCC
ATACCCCTTACTTCGGCAACGCTGGGCGGATTGGCCCTGCCGCTGCAGCAAACCATCGACGCCATCGAATTGCCGGCA
ATCTCGTTCAGCCAATCCATACCCATCGACATTCCGCCGATCGACATCCCGGCCTCCACTATCAACGGAATTTCGATG
TCGGAGGTCGTGCCGATCGATNTNTCCGTCNACATTCCGGNGGTCACCATCACCGGCACCAGNATCGACCCGATTCCG
CTGAACTTCGACGTTCTCAGCAGCCCGGAACCA

TTAACCCCGTGGCCTCTACGCCGCCTNCGGGTCGAACATGCATCCCGAGCANATGCTCGAGCGCGCACCCCACTCGCCGATGGCCGGAACCGGCTGGTTACCCGGGTGGCGGCTGACGTTCGGCGGCGGAGGACATCGGCTGGGAAGGGGCGCTTGCCACCGTCGTCGAAGACCCAGATTCGAAGGTGTTCGTCGTCGTCTCTACGACATGACCCCGGCGGACGAGAAGAACCTTGACCGGTGGGAAGGACCTCGAGTTCGGCATCCACCANAAGATCCGATGCCGCGTT

Clone Rv308

CTCAAGCTTGATTTTGATCATCATGGATGATCATCACCCGAAGTGTGGTAGCCGCAGTGGTTATCGTGGGTACCGTCG
TGCTTTCCATGGGCGCCTCTTTCGGGCTTTCCGTATTGGTCTGGCAGGACATTCTGGGTATCGAGTTGTACTGGATGG
TGTTGGCGATGTCGGTGATCCTGCTCCTGGCGGTGGGATCCGACTACAATCTGCTGCTGATTTCCCGGTTGAAAAANG
AAATTGGGGCCGGATTGAACACCGGAATTATCCGTGCCATGGCTGCCGGGGGAGTGGTGACGGCTGCCGGCATGG
TGTTCGCCGTTACCATGTCGTTGTTTTGTGTTCAGCGATTTTGCGAATTATTGGTCAGAT

CGNCCAACCGAATTGGTTTTCGGCGCCNTCGGTGAGGACGGCGTGCTGCGGGTGCTCAACGACGACGTCGTCCGCGGGAC
ACACCTCGATGCTGCCGCCATGGACGCGGTCGAACGCAAGCAGCTGATCGAGCTACAACGCCGCGCGGAACGCTTCCG
CCNCNGGCGTTACCGCATCCCGTTGACCGGGCGGATCGCGGTGATCGTCGATGACGGCATCGCCACCGGAGCGACGGC
CAAGGCGGCGTGCCAGGTCGCCCGGGCGCACGGTGCGGACAAGGTGGTGCTGGCGGTCCCGATCGGCCCANACGACAT
CGTGGCGAGATTCGCCGG

Clone Rv309

CGTGACTGCCACCGGGGCCACTCCGCAGAATCTGTACCCGACCAAGATCTACACCATCGAATACGACGGCGTCGCCGA CTTTCCGCGGTACCCGCTCAACTTTGTGTCNACCCTCAACGCCATTGCCGGCACCTACTACGTGCACTCCAACTACTT CATCCTGACGCCGGAACAAATTGACNCAGCGGTTCCNCTGACCAATACGGTCGGTCCCACGATGACCCANTACTACNT CATTCGCACGGANAACCTGCCGCTGCTAGAGCCACTGCGATCGGTGCCGATCGTGGGGAACCCACTGGCGAACCTGGT TCAACCAAACTTGAAGGTGATTGTTAACCTGGGG

Clone Rv30

::::::::::Rv30SP6.seq::::::::::

ATACTCAAGCTTCCGCTGGGGCCTGTTCAACCATGGCGATCCCGTTGGTCCCGGACATCCCGAACGAGGACACCGCGA CCCNCTTCGGTGTGTGATCATTACCGTTGGGCCACTGCGTAACCGCTTGCGGCACAAAGAGCCCGGTCTCGACGTCGG AAAGCTCATCGGGCACCCGATTGAAATGCAGCAGCGGCGCACCACCCCGTGCCGCAGTGACAGAATTGCCTTGATCA GCCCGACGGTCCCCGCCGATGCCGTGCTGTGCCCCATGTTGCTCTTGGCCGATCCAAGCGCGCAGGGGGTGCCCGCG CATACACCCGCGCCAGGCTGCGGTACTCAATCGGGTCGCCGATTGGCGTACCGGTGCCGTGCCCTCCACCACACCGA CCGTTTCGGGCTG

GGGCATATGTCCANAACGGACGNGGCCGGTTTCNTCGATGCNGCCGGGGTCCGCGACNTGCGGACNCNCNGNCACACC ATCCGCCAGTCCGCGTGGCGTCCCGCCGCGACTCTGCCTCGGCCGCCCA

Clone Rv310

CTCAAGCTTTGNCGACGATCGGGCGATGTCGATGANAGGAAACCCCAGCGCACAACCGACNATTTTGGCGTAGCCGGC GGACNTCTGCTCGATTCCGATCACGTCGGCGCTCGCATCGAGCATGGCGCCGACGGCTAGCAGCGATCCGCCGTC GTCGAGGAACACGACCCGTACGCCCGGCCGTAAGCCGCCCCAGGATTCGGCGAAAAACCGTTCTACGTGGCG GGTGTACTGGGTGTCCAATGATTCGTGGGGTGCGTAGGCGTCGCTCGAATCGTCGACATAAATGCCGTCGGCCCGCAT CGCGTCAACACTCCCGGGTGAGTGGAATANCACTTGCCGA

TCCAACGCGGTGACAGATTTGTCTATCCTGGACCTGACGGTGAGGTCGAAGTTTTCCAGGAATTCGGCAAAATCGGTA AGAGCCTGAAGAATTCGGTATCGCCGGACGAAATCTGCGACGCATACGGGGCAGATACGCTTCGGGTTTACGAGATGT CGATGGGGCCGCTGGAGGCTTCACGTCCATGGGCCACAAAGGATGTTGTCGGCGCGTACCGTTTTCTGCAGCGGGTGT GGCGCTTGGTCGTCGACGACCACACCGGCGAAACTCGGGTGGCTGACGGCGTGGAACTCGACATCGATACGCTACGGG CGTTGCACCGCACCATCGTCGGCGTGTC

Clone Rv311

CTCGTCCTTGACTACGCCCAGTATCGAAANCCTCCTGTGCCGGTNCGCTAAACACCCCGGCGGACACTCANACGGTGCT GGTGGTGCGCATGGCACCGCGGGCAGCAAAGCGCACTTCTCCGGGGACGACAGCAAGCGACCGCTAGACAAGAGGGG TCGTGCGCAGGCAGAAGCGTTGGTACCACAGCTGCTGGCGTTCGGCGCCACCGATGTTTATGCCGCCGACCGGGTGCG CTGCCACCANACNATGGAGCCACTCGCCGCGGAACTGAACGTGACCATACACAACGAGCCCNCCCTGACCGAAGAGTC CTACGCCAACACCCCAAACGCGGCCGACACCGAGTGCTGCAGATCTTCG

GTATCGCCTCCNCCTTTGGCCACCAGCAGCCACAGCGCGGTTCGCGGACCGAACGTGGACATCAATAGCCCGGAATCG GTGTGCAAGTTGGTAAACGGTGTTGATCCCAAGCTTTGCCAGCCTTTTCGTAGTCTTTGGGCCCCACACCCCACAGT GCTTCGACGGTACGGTCACCCATGATGGCCATCCAGTTGGCATCGGTGACTGATAGATGCCAGCTGGTTTCGCCAAC  $\tt CCGGTAGCGATCTTGGCGCGCTGCTTGTTGTCACTGATACCTATCGAGCAAGACAGCCCGGTTTGCGACAAGATGACT$ TTTCGGATCTCTTCNGCGAACTTCCAATGGGGGTCTCCGGGANT

Clone Rv312

CTCAAGCTTTTGGTCTAGCCGGCCGAGCACGATACGGGTGTCCTTGGCCACCGGCGGCGGCTGTCCGGGAAATGGCGG CGCGAAGCTGAATCCTCCAACCGGGTTGTCGATCCGGACAGGTTGGGGTGCGTTTGGGGCAATGACAGGTGGCGGCGG TGCGTTCGGGTCGGCCGGAGGTGCTGCGTTGGGATCNCCCGGCTGGGCATTCGGCNTNTTGGCGGCCGGCCGGTGG TGGGGGGCAACANGTGTCCCGGTGCGGGTGGCGCTGC

ATCTGTACCCGACCAAGATCTACACCATCGAATACGACGCGTCGCCGACTTTCCGCGGTACCCGCTCAACTTTGTGT CGACCCTCAACGCCATTGCCGGCACCTACTACGTGCACTCCAACTACTTCATCCTGACGCCGGAACAAATTGACGCAG CGGTTCCGCTGACCAATACGGTCGGTCCCACGATGACCCAGTACTACATCATTCGCACGGAGAACCTGCCGCTGCTAG AGCCACTGCGATCGGTGCCGATCGTGGGGAACCCACTGGCGAACCTGGTTCAACCAAACTTGAAGGTGATTGTTAACC TGGGCTACGGCGACCCGGCCTATGGTTATTCGACCTCGCCGCC

Clone Rv313

GCTCACCGGTTCGGAACACGTATCGAAAAACGTCGCACTGCTGGCAGATGGTATCTCCGATGTGGTTGTAATTTGTA TCCCAACTCTAACTGTGCTATCGGATCAGCGTGAATATCGANATATTGCGAATGCGATGACAGGCCGCCATTCGGTTT ATTCGCTTACGCTTCCCGGGTTCGATTCGTCTGATGCACTGCCGCAAAACGCGGATATGATTGTTGAAACCGTATCTA ACGCAATTATTGATGTGGTAGGCGGCAGCTGCCGTTTTGTGCTGTCGG

#### Clone Rv314

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### Clone Rv315

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ACTCAAGCTTGAGATTGGCGTCAACGGGTGTCGGCACCGGCGTCCTGCAGTTGGTAGGCCTGCAGTTTGTGCATCAGG CCGATGCCGCGGCCCTCGTGGCCACGCATGTACANCACCACGCCGCGCCCCCTCACGGGCGACCATCGCCAGCGCGCG TCCAGCTGAGGCCCGCAATCGCAGCGGCGTGACCCAAACACATCGCCGGTCAAGCACTCCGAATGCACCCGGACCAGC ACGTCG

TCACCGTCGGCGTTGGGCCCGGCGATCTCGCCGCGGACCAGCGCGACATGTTCCACGTCCTCGTAAATGCTGGTGTAA CCGATGGCGCGAAACTCCCCATGACAANTCGGAATCCCGCGCCTCGGCGACCCCGCTCAATGTTGCTTCTCNTGCTTG

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## Clone Rv316

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ACCGGGGCCACTCCGCACAATCTGTACCCGACCAANATCTACACCATCGAATACGACGGCGTCGCCGACTTTCCGCGG
TACCCGCTCAACTTTGTGTCNACCCTCAACGCCATTGCCGGCCACCTACTACTGCACTCCAACTACTTCATCCTGACG
CCGGAACAAATTGACGCNGCGGTTCCGCTGACCAATACGGTCGGTCCCACNATGACCCANTACTACATCATTCGCACG
GANAACCTGCCGCTGCTAAAGCCACTGCGATCGGTGCCGATCGTGGGGAACCCACTGGCGAACCTGGTTCAACCAAAC
TTGAAGGTNATTGTTNACCTGGGCTACGGCGANCCGGCCTNTGGTTATTCCACCTCNCCGCCCAATGTTTGCNACTCC
CGTTCGGGGTTGTTCCCNNAAGGTCAACCC

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CGCTCAAGCGCNTGAGGCCGAANCGGCTGGTTACGACTCCCTGTTTGTGATGGACCACTTCTACCAACTGCCCATGTT
GGGGACGCCCGACCAGCCGATGCTGGAGGCCTACACGGCCCTTGGTGCGCCACGGCGACCGAGCGGCTGCAACT
GGGCGCGTTGGTGACCGGCAATACCTACCGCAGCCCGACCCTGCTGGCAAAGATCATCACCACGCTCGACGTGGTTAG
CGCCGGTCGAGCGATCCTCGGCATTGGAGCCGGTTGGTTTGANCTGGAACACCGCCAGCTCGGCTTCGAGTTCGGCAC
TTTCAGTGACCGGTTC

### Clone Rv317

# ::::::::::::Rv317SP6.seq:::::::::::

CTCAAGCTTGCGTTCGATGAAGTAGTCGTCGGTCAGCGCCCTCTTCGAGCTCCTTGGCGATGCCCAGCAAGGAGTC
ATCGCCGCCGAGCTTGGCCAGGATCTTGTCGGCCTGTTCCTTGACGATGCGGGCCCGCGGATCGTAGTTCTTGTAGAC
ACGATGACCGAAACCCATCAATTTGACCCCGGCCTCGCGGTTCTTGACCTTGCGTACAAACTCGCTGACGTCGTCGCC

Clone Rv318

CTCGAAGCTTTAACAGCATCAACCCCGCCCCGCACCAGCACCACACNATGTCGATGCCATCGAGGTGAATGTCGAAC
TGGCGCAAACCATCGGCGACCGCGACCACCGGCAACATGGGTACCGGCGATTTCCGGTGCCAATGCCGACCCGACGGG
CCGCTCTCACCGCAGGTGACCTCGATCACCGAGACCANCCGGCCGTTNTNNTCACGCACCCCTACCGTGTCACGCCCA
AAACGGCGCTGGTGGTCGATTGCCGGAGTGCACCCCNCACCCAGTGTCGTGCCCGGATCC

Clone Rv319

Clone Rv31

GCGCGTNGAACTGATAGGTGCGGCCCGGCTCGAGCANGCCGGCCATTTGTTCGATGCGGTTACCGAAGATCTCTTCGG TGACCTGCCCGCCGCCGGCCAGCTCGGCCCAGTGCCCGGCGTTGGCCGCCGGCGACAATCTTGGCGTCCACGGTGG TCTGGGTCA

Clone Rv321

::::::::::Rv321SP6.seq:::::::::::

CTCAAGCTTCAATACAGAGTTATAAACTGTGATAATCAACCCTCATCAATGATGACNAACTAACCCCCGATATCAGGT CACATGACGAAGGGAAAGAGAAGGAAATCAACTGTGACAAACTGCCCTCAAATTTGGCTTCCTTAAAAATTACAGTTC AAAAAGTATGAGAAAATCCATGCAGGCTGAAGGAAACAGCAATAACTGTGACAAATTACCCTCAGTAGGTCAGAACAA

Clone Rv322

Clone Rv327

CTCAAGCTTTCGGCGGAGACGGACANNTTGCGAACATTGATGACAAAATAGAAATCATTGATGGTTTGAGTCACCAGG CCGATCAAGCCTTCGCCGAGCCAAATTCCAATCAAGAGGCCCAAGCCCGTACCAATCAGCCCGGCAACGAGGGATTCC GTCATTATCAGCCAAAATAACTGCTCTCGGGTTACACCCAAACAGCGCAATATGGCGAAAAACGGTCGCCGTTGCACG ACATTAAATGTCACGGTATTG

AGCTTAACTGCTCCCTAATACCTGGGGCTGTGCCTGCGGTGTATGCACGGCATACGGACATCCNTCCCCTGAGACCCN CGGTCTAATCAGCCACGTGTCCACCATCAGGGGTCAACCCCGGCCAAGGGCGACGGCACCCCAAGTTCGCCGACCGTT AACCTATTGCTGTGAGCTTCATTTGCTGCGAGCAAAACAGTTGGTCGGCCGTTAGGAACTGAATTGACACTCAACCGA TTTGGTGCCNCCGTAGGTGTCCTGGCTGCGGGTGCGCTGTGTTGTCCGCGTGTGGTAACGACCACAATGTGACCGGG GGAGGTGCAACCACTGGCCACGCGTCCGCGAATGTCTATTGCGGGGG

Clone Rv328

GCACCAAGGCCCCACACGTCACCCTGTGACCTCCTGCGCCGACCCCGACGCCCGAGGTCCTGGCCGTTACCACCTGAACGGGCGAGCCGGGAGTCTGGTACGACAACAAAGAGCAAGGTGCATGGGCGGAGTTGTTCCGCCACTTCGTCGATGACGGGGTCNATCCATTCGAGGTCCGTCGCCGCGTCGGTCGAGTGGCGGTCACACTCCAGGTACTCGACCTCACAGACGAGAGACGACTCGATCCCATCTAGGTGTGGACGAAACAGATCTTCTGTCCGA

Clone Rv329

GTCCTCGAGTGCCGCCGTCGNCACNCCCAGCGCCCCGCGCGCCACTTGGATGCGACCCGTTTCAAGTCCCTTCATCAT CTGCGAAAAGCCTTGACCCATGGCTCCGCCCAGGATCGCCGAGACCGGCACCCGGAGGTTGTCGAACGACAGCTCGCA GGATTCGACGCCCTTGTAACCCAACTTCGGCAAGTCCCGCGACACCGTGAGTCCCGGCCCGGGTTCGACGAGCACGAT CGACATGCCTTGGTGCCGCGGTGTGGCGTTCGGGTCGG

Clone Rv32

GGCATACCAATGTGGACTTCTGCTCACCCACGATATCCGTGGTCTGATCCGCTGCTGCGGCGGGCTGCNACCTGCNTC
TCNGCGGCACCCGTNACTACATGGCNCGCGCCGCACGCATACGTCGCGGGGGGACCCACTCCNACTGGTCGACGGTGC
TGGCCGCGTGTCCGCANGTCCCNAACCCGGCCGCACCGACGAAACCGGCCGCCGTCCGTTCTGGACCAACGCTCATGT
GCCGTCGGGGTCCATGCTCGACGCCATCGAGACCGTAACCAGCGTCCTCGAGCGGTTCGCCTCCGGCTTCCGTGACAT
CTTCGTGGCTGCTCGCGCCGTGCCGCCGCGGATGGTCGACCACAACGCCAACCACCTCGGCGTGACATCACCGTC
CGCGCCACTCGACCTGGCGCGCGATCGCGCCCC

::::::::::Rv32T7.seq::::::::::::

GTGAGCAGACCTACGCCNCCTGGTTGCGCCAACTCGGTACCGATCATGGCGCGCNGCCTGTCGTCACCGATACCCAGC GAACAAGACAGCCCGGTCCGCGACAAGATGACTTTCCCGATCTCTTCGGCGACTTCCATGGGGTCGTCCGGAGTCCCG GGCGCCACCGCGAGGTAACCCTCGTCTCAGTCCCATACGCGACCGGGTATCCACGTCGCGAACAACGCCACCACCTC CCCAGACGCCNCGTTGTACGCGGCTGGGTTCCACNGCAATAAGTGGCCTCANGGCATCGTCCGGCGGCGGTCCNCAAC GCA

Clone Rv330

::::::::::Rv330SP6.seq:::::::::::

CTCAAGCTTGAGGTTAACTTTGAACGGATCGAGCTGGACGTTCGAGACGTGATCGGGCCGAACCTGAATTGTCCGGT
AATGCCCAACGCAAAAAGCAGGGTGGTGGCCGGGGCGGTGAAACCGGCGTCGGCGCACCGTCGAAATCTATGTGGAT
TGCCGGAATGGGGATGTCCGGCACGGCGAAACCGTAGTTCGCTTGTCCCGTGAGGCCCAGGTGGATGGGGGGAAAGAT
CCTGGTGTCCGGGATAATAATGGGGCCGATGCCGCCGGTTGAAGTCCACTGGATCGGGAATCTTGATCCG
ACGTTCAGGCCGAACAGGCCCTC

CGGCGACGTCGCGATACGCCGAGCAGTTGGGAATCGCTCTGCAGCAAACCAATATTCTGCGCGACGTTCGAGAGGACT
TTTTGAATGGACGGATCTACCTGCCGCGCGACGACGACTGGACCGATTAGGCGTACGCCTCCGCCTGGACGACACCGGGG
CACTCGATGACCCCGACGGACGGCTCGCGGCCTCGCGTTCAGTGCCGACCGCCGCAGACTGGTNTTCGCTGG
GACTGCGGCTGATTCCACACCTCGACCGCCGCAGCGCTGCTGCTGTGCGGCCATGTCTGGCATCTACCGCCGTCAGC
TCGCCTTGATCAGAGCATCGCCGGCGGTCGTCTA

Clone Rv331

::::::::::Rv331SP6.seq:::::::::::

::::::::::Rv331T7.seq:::::::::::

Clone Rv333

Clone Rv334

Clone Rv335

CNTCATGATCATCACCCGAAGTGTGGTAGCCGCAGTGGTTATCGTGGGTACCGTCGTGCTTTCCATGGGCGCCTC
TTTCGGGCTTTCCGTATTGGTCTGGCAGGACATTCTGGGTATCGAGTTGTACTGGATGGTGTTGGCGATGTCGGTGAT
CCTGCTCCTGGCGGTGGGATCCGACTACAATCTGCTGCTGATTTCCCGGTTGAAAGAGAGAAATTGGGGCCGGATTGAA
CACCGGAATTATCCGTGCCATGGCTGGTACCGGGGGAGTGGTGACCGCCGCATGGTGTTCGCCGTTACCATGTC
GTTGTTTGTGTTCAGCGATTTGCGAATTATTGGTCAGATCGGTACCAC

Clone Rv336

GCTGGTAGAGTCGCTGACCGGTGCAGGTTTCGACAATGTGGTGCCGGTTCGGCGGCTACGTGCCATCGAGACACTGGC GCAGGCTATCGCACCCGTTATCGGCTACGAGCAAATCGCGGTATGCGTTCTTGAGCATGAGTCGGCGACCGTCGTCAT GGTCGACACCCCACGACGGAAAGACGCAGATCGCCGTCAAGCATGTGTGCCGCGGATTATCAGGACTGACCTCCTGGCT GACCGGCATGTTTGGTCGCGATGCCTGGCG

Clone Rv337

Clone Rv338

TACTCAAGCTTCGCGAGATCCGGATGCCACTCACGCTGGACAAGACCTTCACAAAATCTGAAATCCTGACCCGATACT TGAACCTGGTCTCGTTCGGCAATAACTCGTTCGGCGTGCAGGACGCGCGCAAACGTNCTTCGGCATCAACGCGTCCG ANCTGAATTGGCAGCAAGCGGCGCTGCTGGCCGGCATGGTGCAATCNACCAGCACGCTCAACCCGTA

CCCACGACTTTCTCCTCGATCAGTTGGATTTGTACGAAGAGGCAACGAAAGCAGTGATCCTCGGGATGGTCGACGCCTACATCGACCCGCTTCACGCCGCACAGCCTGCTAGATGCGCTGGGCGAGCAGGTCCCACAGTTCGCCGCTAAGGCACGGGTCTGTTCCCGTCCGGATCGCCATTCGGCCTCGGCGTCCTGCTCCCATTCGATCAATAGGGCTGGCAGCTCCGTCGGCAGGGGGCCTACGCCTCACCCGTCACG

Clone Rv339

CTCAAGCTTATGCGCCGCCGAGGTCTGCTCACGGCAACCCCTGAAGTTTAGGGGACNACCTACTCAGCGCAAAAT
TTCGCTAATGTGAGTCCGCCCCACCAGGGGNANATCAACCCATGTCGATCATGATCTACCCGGATACCGGATTGGCG
TAGCGCCCACGATCGTCNAAATNTCCGCCTGAATCATCGGATAGCTGATCCGGCGTCAACGCGTTTTGANTTCACCGC
GCAACAGCCGCCCAGGCCGGCCCGCANCGANCCGATCTCNTCGGGCCCCCAATCTTNTCG

GTGTGTGGTGGAACCCATCTGAGCAGTGTGCCAAACCGGGGCAGACAGCTCCCAATTGACGTGAGCCCGCTCACTTGC
TGGGTAAGCGTC

Clone Rv33

CTTTACACTTCCTGCATCCGGCTCGTATGTTGTGGGAATTGTGAGCGGATAACAATTTCACACAGGAAACAGCTATGACCATGATTACGCCAAGCTATTTAGGTGACACTATAGAATACTCAAGCTTGGGCGTGACGGCCACCGGGGCCACTCCGCACCATCTGTACCCGACCAAGATCTAC

Clone Rv340

CNCAAGCTTGCGGATGTTACCCCTGACAGCCTGAACTATGTCNAAACACACGGCACCGGAACGGTGTTGGGGGACCCC
ATCGANTTCGAGTCGCTGGCGGCCACTTATGGCCTGGGTAAAGGCCAGGGCNANAGCCCGTGCGCATTGGGGTCGGTC
AAAACCAACATCGGCCACCTGGAGGCGGCCGCCGGTGTGGCTGGATNCATCAAGGCGGTGCTGGCGGTGCAACGTGGG
CACATTCCCCGCAACTTGCACTTCACCCGGTGGAACCCGGCCATCNACGCGTCGGCNACGCGGCTGTTCGTGCCNACC
NAAAACCCCCCGTGGCCGGCGC

GGAACCGGTAACCAGATCAGCTCGTCGACCTCACTGCCGGGGGTGAATTCCCCACCGGTGCTGCCCAGTAG TGCACCTTCTTGACGCCTCGAAAAGGGGAGTCGGTCGGGTAGGTCACCGTCAGGAGCCGCCTACCCAGGTTGGCGCNA TAGCCGGTCTCCTCGAGTATCTCCCGCACCGCCCCCACCGGTGCGGTCTCACCCANATCCACTTTGCCCTTGGGCAGC GACCAGTCGTCGTANCNGGGGCGGTGAATGACAACGATCTCGACCGGCCCTTCCN

Clone Rv341

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Clone Rv343

CCACCCGTGTAATTTGGGATGGGCNAAAAGGCNAAGCACCGCGTGGCCACGAACGCCGGGAGGGACAATCTCGGGCGG CTAGGGCTTCTCGCGGGAAGGCCCGAACGTACGGCGTTTCAACACGTCGCGTCGCCCTCCGACCGCGAACATTCGGGG ATGGCAGCAACCTGGTAGCACCCTGGCCGGGCGATGATCTGCAGCGTCGCCGCGGGTAGTCGCCCCCGGGCGGCTAC AGTCTGAAACGCGATGACCATCGATGTGTGGATGCAGCATCCGACG

Clone Rv344

CCGGGGCCACTCCGCACATCNGTACCNNACCAANATCTACACCATCGAATACGACGGCGTCGCCGANTTTCCGCGGTACCGCTCAACTTTGTGTCGACCCTCAACGCCATTGCCGGCACCTACTACGTGCACTCCAACTACTTCATCCTGACGCCGGAACAAATNGACGCNTCGGTTCCGCTGACCAATACGGTCGGTCCCC

Clone Rv346

NCTGGCCTTTGGTCCACACTAANACAATACTCAAGCTTCCGGCCGCAGAGCCGCCAACTCACGATATCGTTAACCGAT ATCCCGAGCCGATAGCTGGCGGGCTCGGGTGGTGGCCAGCGGCGCGCTGCGACNAAAGGTGTGACCGTCATGAAACAGAC ACCACCGGCGGCCGTCGGCCGTCACCTGCTCGANATCTCAGCATCCGCAGCCGGTGTGATCGCGCTTTCGGCGTG TNGTGGGTCNCCGCCCGAGCCCGGCAAAGGCCGGCCCGACACACCCCGGAAC

Clone Rv347

Clone Rv348

CNCCAGCTTGATTGGTCTGGTTGCATTGGCCAGCTGCGCGÁGCCTGGCTCACTTCAACTACGACGACCGCAAACAATT GCCGCCTTCGGATCCGAGTTCGGTTGGGTACGCGCGCAATGGAGCACCATTTCTCGGTGAATCAGACTATTCCTGAGTA CTTGATCATCCACTCTGCACACGACCTGCGAACCCCGCGCGCCCTTGCCGACCTGGAGCAGCTGGCGCAACGTGTGAG CCAGATCCCAGGCGTTGCCCATGGTTCGCGGTGTGACCCGGCCAAACGGGGAAAC

Clone Rv349

TCGACGGTTTGGCGGCCTTAAATGCACTGAGGTCGTCAATTGACCCCACAGCGGAAATGCCGACTATTCGCAGGCCTC
CTTCGCCTTGGCTGCCGGAGAGGGGCTCCGCGGGAACCGCATGCAGGTATATGACCTCGGTTTCTCGGGTGCTACCGC
GTGCCTTGTNTANGATNANCTCGGCGTTGGAATTGTCCAGCCGGCCCAATTCATCGAGCGCANATTCGTACACNTGGC
CGGCGGCGACATACGCTTCACCGTGGATCTGCTCCACACGGACCGCCCTGTCGGGATCCTGCTCACGGGTAANGGAAC
TTACGTGGCACTCGG

Clone Rv34

 ${\tt GACCACGCCAGGCTAATCACGTGACGCTACCGAATACCCTNCCTAGTGGTGCAGGCTCCCGCTGGAAATGGCCCTGTACCAACTCGCGCACCGGTGCCAG}$ 

 $\tt CGGCACCCGTTGAGCCGTCGCCGTGGCCGGTGGAACTGGCCGACGAGGGACTGATCGTGCTGGGCAAATTGGTCGATGGCACGCTGGCCGCCGATCTGAAGGTCN$ 

Clone Rv350

CTCAAGCTTGCCGTTACCCCGACTTCCGGAGGGACACCATGAGCACCGCCAGCCGAGCACGAGGCCAAACTCCGCCGA CGCAGGCCGGTTGGACTTGTCGTGCTGGACAAGGGGTTTAGCCGCCGAAGCAGTGACGTACATCGGCGAAAAGCAGTT CGCCTGTCGACCGACGGGGCNNACCGTGAGGCTAGGGAAGCGAGGAGCACATGGCCGCCGACCCGCAATGTACACGCT GCAAGCAAACCATCGAACCCGGATGGCTATNCNTCACCGCCCATCGCCGCGGT

CATGTCGCGCACATCCAGGACTTCTGGGGGGATCCGCTGACAGCGGGGGGATCCCAAAGTGCGGATGATCGGGCCGCC TACGTCGTGGTGTACCTCGTCGGTAACAACGAAACCGAAGCGTATGACTCGGTCCACGCGGTGCGGCACATGGTGGAC ACCACACCGCCACCGCGCGGGTGAAGGCCTATGTCACCGGTCCGGCAGCCACTCAATGCCGACCAGGCCGAGGCCGGA GACAAAAGTATCGCTAAGGTCACCGCGATCACGAGCATGGTGATCGCAGCCAATG

Clone Rv351

:::::::::::Rv351SP6.seq:::::::::::

ATACTCAAGCTTCGGTACGGTGGCGGGCCGTGCTGCTGGCCGCGGTCGCGGCGTGCGGGCCTGCGGTCTCGTTTACN
AGCTCGCGCTGCTGACACTGGCGGCNAGCCTGAACGGCGGCGGGATCGTGGCCACCTCCCTGATCGTCGCGGGCTACA
TAGCCGCGCTGGGAGCAGGCGCCTTGCTGATCAAGCCGCTACTTGCACACGCGGCCATCGCGTTCATCGCCGTGGAGG
CGGTGCTGGGCATCATCGGCG

Clone Rv352

TACGCTGGCGCTGGAGGAGCCANNTACAACATCCACGCCAATGCTCTTGCCCCGATCGCGGCGACCAGGATGACCCA GGACATCCTGCCGCCCGAAGTACTGGAAAAGCTCACACCCGAGTTCGTCGCACCGGTGGTGGCCTACCTGTGCACCGA GGAGTGTGCCGACAACGCATCGGTGTACGTCGTCGGTGGCAAGGTGCAGCGAGTTGCGCTGTTTGGCAACGACGG CGCCAACTTCGACAAACCGCCGTCGGTACAAGATGTTGCGGCGCGGTGGGCCGAGATCACCGATCTGTCCGGTGCGAA AATTGCTG the first that the second of t

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Clone Rv353

GCTTTTCCCGTCCGTCNNCGCTCAACCGCGTGAGGCCGAAGCGGNTGGTTACGACTCCCTGTTTGTGATGGACCACTT CTACCAACTGCCCATGTTGGGGACNCCCGACCAGCCGATGCTGGAGGCCTACACGGCCCTTGGTGCCACGGC GACCGANCGGCTGCNNNTGGGCGCGTTGGTGACCGCAATACCTACCGCAGCCCGACCCTGCTGGCAAANATCATCAC CACGCTCGACGTGGTTAGCGCCGGTCGAGCCGATCCTCGGCATTGGAGCCGGTTTGANCTGGAACA

Clone Rv354

CCGACGCCGTCGTGGCCACCAACACCCCGACCAGCACCGTGACCCGGACCGGGTGCCGCGCAACCGGTCTTGGCCA
ATTGCCGCGGCACCAAGCCGTCGCGCCCATGGCGAACAGCACGCGCATTGCCCGAGCATCAACACCATCACCACCG
TGGTAAGCCCGGCCAGCGCGCGAGAGTGATGCCGCTGGCCCAGTACACCCCGTTGGCCTGGAACGCGGTGGCCA
GATTTGCCGGCCCGCGGCCCGGTACGGTCCGCAGTTGGGTGTATGGAACCATGCCCGACAGCACCACCG

Clone Rv355

TTNACTGGCCTTTGGTCCACACTAGACAATACTCAAGCTTCCAGGACATCGTCATCGCGACCAAAAACCGCGAGCTAGG TCGGCATCCGGGAAGCATCGCGACACCGTGGCGCCGAGCGCCGCTGCCGGCAGGCCGATTAGGCCGGCAAATTAGCCC GCCGCGCTCCCGGCTCCGANTACGGCGCCCCGAATGGCGTCACCGGCTGGTAACCACGCTTGCGCGCCTGGGCGGCG GCCTGCCGGATCAGGTGGTAAATGCCGACA

NGACGTCTTCCATCCGCGCGTCGTTTTGGCGGGTTGGCCACAGCAGCCCGCCGGTGACGGCGACGATGCTGGGCTGGT TGCGGCCCTGCGCCACCGCGGCTTGCATGCTGGTTGGCTGTCTTGGGACGATCCCGAAATAGTCCACGCGGATCTGGT GATTTTGCGGGCTACCCGCGATTACCCCGCGCGCGCTCGACGAGTTTTTTGGCCTGGACTACCCGCGTGGCCAATCTGCT GAACTCGCGGCCGGTGGTGGCCTGGAATGTCGAGCGCCGTTACCTA

Clone Rv356

CTTCCTCTGAGTACCNCCCGTNTACTTTGGGATGGGTAAAAAGGCGAATCNCCGTTTGGTCACGAACGCCGGGAGGGACATCTCCGGGGGGCTGGGGCCTCTCGGGGAANGCCCGAATGTACGGTGTCTCGACACTTCCCNTCCCCTCCG

GAGCATCGGGACNTACGGAGTCAACTACCCGGCCAACGGTGATTTCTTGGCCGCCGCTGACGGCGCGAACGACGCCNGCGACCACTTCAGCAGATCGCCAGCGCGTGCCGGGCCACCACGAGGTTGGTGCTCGGCGGCTACTCCCAGGGTGCGGCCNTGATCNACATCGTCACCGCCGCCACCACTGCCCGGCCTCGGGTTCACGCAGCCGTTGCCGCCCCNCAGCGGACGATCACNTCGCCGGATCGCCC

Clone Rv357

TACTCATGANCATCCTTTAATCANNGCTTTGCGTTTTTTTATTAAATCTTGCAATTACTGCAAAGCAACAACAAAATCGCAAAGTCATCAAAAAAACCGCAAAGTTGTTTAAAATAAGAGCANCACTACAAAAAGGAGATAAGAAGAGCACATACCT

### Clone Rv358

::::::::::Rv358SP6.seg::::::::::

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:::::::::Rv358T7.seq::::::::::

CATGGTGGCACTGTAGCGACGTGCTGCAATCAAGGTCATGCCCGACTCTGGTCAGCTCGGANCCGCTGACACCCCGCT
AAGGCTGCTCAGCTCGGTGCATTACCTCACCGACGCGAACTCCCCCAGCTTTACGACTATCCGGATGACGGCACCTG
GTTGCGGGCGAACTTCATCATCAGCTTGGACGGCGGCGCTACCGTCGATGGCACCAGCGGGGCGATGGCCGGGCCCGG
CGACCGATTCGTCTTCAACCTGTTGCGTGAACTTGCCGACGTCATCGTGGTCGGCGTGGGCACCGTGCGCATTGAGGG
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## Clone Rv359

:::::::::Rv359SP6.seq::::::::::

TACTCAAGCTTGCGGGTGATCGCCTTGGTCAACGGCACCGTGATCGGGTCNACCGCACAAATGGACTGGAGC
TTCGGCGAANTCATCGCCTATGCCTCGCGGGGGGTGACGCTGACCCCGGGTGACNTGTTCGGCTCGGGCACGGTGCCC
ACCTGCACGCTCGTCTATCACCTCNGGCCACCGGAATCATTCCCGGGCTGG

GTTGGNGCCTCGTCGGCGAACAGTTCTCGCACGATTTCCGGATTAGCGGGACTGGTCACCAGTTGGGTATGCGGGAAGGCGCTGACGTTCGCCGCGATTAGCTGTTTGATGGACGCGGTGGTGATGTTCTGATCACGGAACTGGCTGTAATAGCCCAGGGTCGCCACGCTTTCATCCGGGCCCGGACCCGGCGCACCGAGCGTGTCGCGCAGGTATGCGACGTGATTTCGCTGAGTCCCCGTACCCGGAGAACT

### Clone Rv35

:::::::::Rv35SP6.seq::::::::::

## Clone Rv360

::::::::::Rv360SP6.seq::::::::::::::

TACTCAAGCTTGGGGTGGCGCTGTCGGTGGTGTGCTTGGCGGCGTCGGTATCAACACCGCCCACGAAATGGGGCACA AGAAGGATTCGCTGGAGCGGTGTCCAAAATCACCCTCGCCCANACCTGCTACGGGCACTTCTACATCGAGCACA ACCGTGGCCATCACGTCCGGGTGTCCACACCGGAGGACCCGGCGTCGGCGGGTTCGGCNAAACGTTGTGGGANTTCC TGCCCCGCANTGTTATCGGCGGCTTGCGCT

Clone Rv361

GCTTGCGGGTGATCGCCTTGGTCAACGGCACCGTGATCGGATCGGGGTCNACCGCNCAGATGGACTGGANCTTCGGCG AANTCNTCGCCTATGCCTCGCGGGGGGTGACCCTGACCCCGGGTGACNTGTTCGGCTCGGGCACGGTGCCCACCTGCA CGCTCGTCAAGCACCTCNGGCCACCGGAATCATTCCCGGGCTGGCTGCACNACGGCGACNTGGTCNCCCTCCAGGTCG AAGGGCTGGGCNAAACAANGCAGACCGTCCGGACAANCGGCACTCCTTTTCCGTTGGCTCTTCGGCCGAATCCGGACG CCNAACCCGACCGGCG

GTTCTCGCACGATTTCCGGATTAGCGGGACTGGTCACCAGTTGGGTATGCGGGAAGGCGCTGACGTTCGCCGCGATTA
GCTGTTTGATGGACGCGGTGGTGATGTNCTGATCACGGAACTGGCTGTAATANCCCAGGGTCGCCNCGCTTTCATCCG
GGCCCGGACCCGGCGCACCGAGCGTGTCGCGCAGGTATGCGACGTGATTTTCGCTGAAGTCCCCGTACCCGGAGAACT
CGAACACGCTGAGGCGCTCGTCACCGTCGTNNCGGCGACCAAGCGCGGCGAGCAACTGCGCAAAATCGTTAAGANAGG
TCGAATCGTTGAAATTCGGCACCACCTGCACC

Clone Rv363

CACAAGACAATACTCAAGCTTCAGGTCAATGTGCNCCAAGCCCTGACGCTGGCCGACCAGGCCACCGCCGCGGANAC GCTGCCAAGGCCACCGCAACACAACAACGCCGCCGAGGCGTTCGCAGCCCAGCTGGTGACCGCCGAGCANANCGTCNAA AACCTCAAGACGCTGCATGACCAGGCGCTTANCGCCNCAGCTCAGGCCAAGAAGGCCGTCGAACGAAATGCGATGGTG CTGCAGCANAANATCGCCGANCGAACCAAGCTGCTCAGCCAGCTCGAGCAG

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CCACCCGTGCATGGTGGCACTGTAGCGACGTGCTGCAATCAAGGTCATGCCCGACTCTGGTCAGCTCGGAGCCGCTGA CACCCCGCTAAGGCTGCTCAGCTCGGTGCATTACCTCACCGACGGCGAACTCCCCCAGCTTTACGACTATCCGGATGA CGGCACCTGGTTGCGGGCGAACTTCATCAGCAGCTTGGACGGCGCGCTACCGTCGATGGCACCAGCGGGGCGATGGC CGGGCCCGGCGACCGATTCGTCTTCAACCTGTTGCGTGAACTTGCC

Clone Rv364

GCTTTCCGCCGATACCCNCCATGTCCCGCACATCCAGGACTTCTGGGGGGGATCCGCTGACAGCGGGGGATCCCAAAG TGCGGATGATCGGGCCGCCTACGTCGTGGTGTACCTCGNCGGTAACAACGAAACCGAANCGTATGACTCNGTCCACGC GGTG

Clone Rv365

Clone Rv366

CTCAAGCTTGACTGGCCACCGGCATGACCACCGACAGGCCCGACTGGTCGTACCACTCGAACGCCGGGGTGTTT

::::::::::::Rv366T7.seq::::::::::::

TTGGTGCCCGGAATGGCGAGTCCCATTTANTCGCTGATTTGTTTGAACAGCGACGAAACCGGTGTTGAAAATGTCGCC TGGGTCGGGGATTCCCTCTCCAAGCAAGAGTAACTGGCCCCAAATAAAGTTACTCGTCGTCTTGCAAAGACCGCTACC

Clone Rv367

GAATTNGCTTTCGGCGCCATCGGCCCAGGACCGCGTGCGGGTGCTCAACGACGACGTCGTCCGCGGGACACACCTCGA
TGCTGCCGCCATGGACGCGTCGAACGCAAGCAGCTGATCGAGCTACAACGCCGCGGGAACGCTTCCGCCGCGGGCG
TGACCGCATCCCGTTGACCGGGCGGATCGCNGTGATCGTCGATGACGGCATCGCCACCGGAGCGACGGCCAAGGCGGC
GTGCCAGGTCGCCCGGGCGCACGGTGCGGACAAGGTGGTGCTGGCGGTCCCGATCGCCCAGACGACACCGTGGCGAG
ATTCGCCGGGTACGCCGATGAAGTGGTGT

Clone Rv368

TAAAGCTTTCGTCAGTTCATNGNGCCCCCGGACCAACAAAAGCATCGGGACATACGGAGTCAACTACCCGGCCAACGG
TGATTTCTTGGCCGCCGCCTGACGGCGCNAACGACGCCAGCGACCACATTCAGCAGATGGCCAGCGCTGCCGGGCCAC
GAGGTTGGTGCTCGGCGGCTACTCCCAGGGTGCGGCCGTGATCNACATCGTCACCGCCGCACCACTGCCCGGCCTCGG
GTTCACGCAGCCGTTGCCGCCCGCAGCGGACGATCACNTCGCCGCGATCGCCCTGTTCGGGAATCCCTCGGGCCGCC
TGGCGGGCTGATGAGCGCCCTGACCCCTCAATTCGGGTCCAANACCATCNACCTCTGCAACAACGGCGACCCGATTTG
TTCGGACGGCAACCGGTGGCGANCGCACCT

CCGGGAGGACCATCNCGGGCGCTNCGGCTTCTCTCCGGAAGGTTCTANNGTNNNGCGTTTCNACNCTTCCCGTCGCCCTGCGACCGCCGAACATTCGGGGTATGGNNGCANCCTGTNAGCATCCNGGCCGGGC

Clone Rv369

Clone Rv36

GCTTCCGGCTCGTATGTTGTGTGGAATTGTGAGCGGATAACAATTNCACACAGGAAACAGCTATGACCATGATTACGCCAAGCTATCTAGGTGACACTATAGAATACTCAAGCTTGAGCCATCGGGCTATCAGCTTGATGTCCCG

CAGGCATGCAAGCTTGTCGTCTATCACATCCGACCACCAACCGCCCGACGGCTCGGCAGAACGCCTCCGCATATGGGT CGACGACCAGCGGGTCGGACTTCTGGGCTGCCAGCGCTCGCGCCGTCGCGACAAACAGCGCGGTCGAACCGACACTCC TTGTGATGTCCCACCTATCACCTTCGGTACGCACCCAATCGACCCTACGCGGCTAGCTCAGCCCCGATCTTCCAGAGC TCCGCCCG

Clone Rv370

Clone Rv371

NAAGCTTTGTCACACCAAGTGTTTCNACCAGNCGCTCCATCCGGCGAAGTGGATACTCCCAGCAGGTAGCAGGTCGCC ACCACGCTGGTCAGTGCGCGTTCAGCTCGCTTGCGGCGCTGCAGCCAGTCCGGGAAATAGCTGCCCTGGCG

CGCTGGNCGCCGGCGCTGGGCTGCGGTAACCAATTACCACAACACTTTTCGGTAGCCGAACAGCGGCGCGTACCAGCG AAATGGCACAGCCACCGCAGTCGCCGACATCCCGCGAAGATGTGGCAGATTTTCGTGCGGTCGAGCCGGCGAAGGCCT AGCGTCATTGTTGCCTGGCCAAGGTTGCTGGGCCCGG

Clone Rv373

GTTCACACCTACCTATGCCNCAATTCNCCGACACGGGTGGCATCAACACGGGCGATAAGGTGGAAATCGCTGGGG TGAACGTCGGGCTGGTGCGCTCGCTGGCAATCCGCGGCAACCGCGTGTTGATCGGATTCTCGTTGCCCGGCAAGACAA TCGGGATGCAAAGCCGGGCAGCAATTCNCNCCNACACCATTCTTGGCCGTAAGAACCTGGAGATCGAACCCCGCGGTT CGGAGCCGTTGAAACCCAACGGTTTCCTGCCGTTGGCGCANACCACTACGCCATACCAAATC

Clone Rv374

CTCAAGCTTTACGCCGACGCCGGCCTACACAACACCAAGGAAACGATTGCCTACTGCCGAATCGGGGAACGGTCCTCGCACACCTGGTTCGTGTTGCGGGAATTACTCGGACACCAAAACGTCAAGAACTACGACGGCAGTTGGACAGAATACGGCTCCTGGTGGGCGCCCCGATCGAGTTGGGAAGCTGATATGTGCTCTGGACCC

TCCCNCATGGGATAACGGGTTTAGATTTCNACAACGGCACCGTGTTTCTCAACAAGCCGGTCATCAGCTGGGCCGGCGACAACGGTATCTACTTCACCCGCTTTCGCCCGTACAAGAAAAACCACTAGGCCACCATCGAGTCCAAGAACAACCACCTGGTCCGCAAGTACGCGTTCTACTACCGCTATGACACCGCCGAGGAACGCGCCGTGCTCAACCGGATGTGGAAGCTGGTCAACGACCGCCTCAACTACCTCACCCCGACCATCAAACCGATC

Clone Rv375

::::::::::Rv375SP6.seq:::::::::::

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TNAACAGCTCGCGGCAGCCCACGACCTGCTGCGTCGGATTGCCGGCGAGATCAATTCCAGGCAGCTCCCGGACAA TGCGGCTCTGCTGGCCCGCAACGAANGACTCGAGGTCACCCCGGTGCCCGGGGTCGTGGTGCACCTGCCGATCGCACA GGTTGGCCCACAACCGGCCGCTTGATGNNNNGTCGGCAAGCCCGGCAGTNGCCAAACCCAGCGTGATCANGCTCGGCT CGCGAGTTCGGCGAANAAGTGGCTCGCCTGATCACCTACCATCGGCCANGATCTGCGTGTCA

Clone Rv376 ::::::::::Rv376SP6.seq:::::::::::::: GCCANCCGGCTTGGCGTCGACTCCCGTTCNGCACATCATACGGTCCCCGGTACTGTCCAACTGCGCCGGTGCGCTAGC ACTNATTATCTCATCCAAAGGACACCGGGCCGGTGGCTGGAATCCCATGGTGCGATCGGCCACACAN CCATGCAAAGATCCGAGGTGTCCCNGATCTAGGGGTCCTCGTCCTCCAGATGATGGAGCAAGTCGGCCC Clone Rv377 ::::::::::Rv377SP6.seq:::::::::::  $\tt CTCAAGCTTCGGCTGCCGGTAACGTCGCTGACCGGTGCAGGTTTCGACAATGTGGTGCCGGTTCGGC$ ::::::::::Rv377T7.seq:::::::::::: GTGT Clone Rv378 AGCTTAGCTTCCCGCCCCGGCAATAGGGCTCCAGCTCATCCGGTGTGACCAGATAGGGGCCCAGGGTGATACCGCTGT  ${\tt CTTTGCCCTTGGCCTGTCCGATGCGCAGCTGGCCCTCCAGCATCTGCAGGTCCCGTGCGGACCAGTCGTTGAAAATGG}$ TATAGCCGATGATCGACCG  $\tt CCNGAACAGAAGCGGNGGTTCCTACCGCGGTGTGCGGCCGGCGCGCGATATCGGCCTTTTTACTAACCGAACCCGATGTG$ GGCTCCGATCCGCCGCGCATGGCATCGACGCCGATCGATGACCGCCAGGCTTACCACCTT Clone Rv379  $\tt CTCAAGCTTGCGCGACTCGACAAGCATTCTTGACAGTTGTTTTGGCTCGGCATGGTTAGCCAAGGTTCTGCGGTCCCA$  $\verb|CCAGATCATCTTGGTCCGGTAGCGCTCGTCCGGGTATGCTGCCGCCGGGATTCTCGCTGCTATTACTCCCCCCGAAGA| \\$ ACGCCACCGGTCCAGCGC GCNAGGCGGTATAGCTTCCCGTCGTACCGGCGACCGCCAGCCGAGAAGCTCGTTTTCCCAGTGTTGCTGGGGATTCTC  ${\tt ACGCTGCTGAGTGCGTGCCAGACCGCTTCCGCTTCGGGTTACAACGAGCCGCGGGGCTACGATCGTGCGACGCTG}$ AAGTTGGTGTTCTCCATGGACTTGGGGATGT

Clone Rv37

GTGTGGAACCGTGAGCGGATAACAATTTCACACAGGAAACAGCTNTGACCTTGATTACGCCAAGCTATTTAGGTGAGG CTATATTAATACTCAAGATTGCGGTCGAGCACATCGGCCCAAGAACCGCCGAAGGCACGGCGGAACGCCTGCGGCACA TGGGGCGACGACCAGCGGGTCGGACTTCTGGGCTGTCCAGCCGGATCGCGCCGTCGCGA

Clone Rv381 CTCAAGCTTTTACGGTGATCGCGCATCACCTGGTTCATGAACTGGAAGCAGCGCAGCGCTTCCTTTTCGGCCGCAACA TGAGCCANCCTCTCGTCGGCGGTCGGGTGCAGGTGCTCGGCCAGCCGCCGACAGCCGCCTGACCCTGAAACCAG CTTCCATATCCCGCGACNAACGAC CTCAGAAGCCGCTAGCTGGTAGAGTCGCTGACCGGTGCACGTGCGCGNCAATGTGCGCTGCCGGTTCGCG Clone Rv382 CTCAAGCTTGCGCTCATCAAGCGCGAACAGCAGGGCGGTCGGCTGGTCGCCATGACGGGTGACGGACCAATGACGCA CCCGCGCTCGCGCAAGCCGATGTCGGGGTGGCNATNAATACCGGCACCCAGGCGGCCCGGGAAGCCGGCAACATGGTC NATCTCCACTCC GGCAC Clone Rv383 GCTTGTCGTATTCCGTGGCACTGTCAGACATATGCGCCGCTCCTCCTCATCGCTGCGCTCGGCATCGTCGCCGGCGGT CATGGCGTCACCCTACCCAAGCCGAACGCGAACGAGAACGTGTTCCATTATTAGGGTGTGAGCACCAATACCAGATT GCTCACCAGGAACTCAC CGATATTCGTCGGCCGCGTTGTCTCGACTGGGTCGCGT Clone Rv384 GACCTCGGCCACCAAGCCGGACGGCGACGGTCGAGGTGGCGATCCGGCTTGGCGTCGACCCGCGTAAGGCAGACCACAT GGTCCGCGGCACGGCCANCCTGCCACACGGCACTGGTAAGACTGCCCGCGTCGCGGCN  $\tt CCGGAAGTCTAGGGGACCGCACCAGGGCAAAATGTCGCTAATGTGAGTCCGCCCCACCAGGGCAGATCAACCCAT$ GTCGATGATGACCTACCCGGATACCGGATTGGCGGT Clone Rv385 AGCTTCAGTTCCTCCACGACGCGTTCCCAAATGAATTTCCCGATCCCACAATCTCGGTTCAGATACAGGTCGCCATAC CCCTTACTTCGGNAACGCTGGGCGGATTGGCCCTGCCGCTG CCGCCTACGGGTCGAACATGCATCCCGAGACCGATGCTCGAGCGCGCACCCCACTCGCCGATGGCCGGAACCGGCTGG TTACCCGGGTGGCGGCTGACC Clone Rv386 GCGGCTGGTTACGACTCCTGTTTGTGATGGACCACTTCTACCAACTGCCCATGTTGGGGACGCCCGACCAGCCGATG CTGGAGGCCTACACGGCCCTTGGTGCGCCACGGCGACCGAGCGGCTGCAACTGGGCGCNTTGGTNACCGGCAAT  ${\tt ACCTACCGCAGCCCGACCCTGCTGGCAAAGATCATCACCACGCTCGACGTTGGTTAGCGCCGGTCGAGCGATCCTCGGC}$  ${\tt ATTGGAGCCGGTTGGTTTGAGCTGGAACACCGCCAGCTCGGCTTCGAGTTCGGCACTTTCAGTGACCGGTTCAN}$ 

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Clone Rv387

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Clone Rv388

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Clone Rv389

GGCGGCTGCGTCGGCGAGATGATCGCCCGGTGCCACCCCGATCCGTGCCTCGGTCAGCGCCAACGTGCTTTCCGGTCCGGCCACCATGTCGCATGCGCCGAC

GCAATCGCCTTGGCGGTCGCCGGGTTGTCACCGGTGATCATCNCGGNGCGGATGCTCATNCGGCGCATTTCGTCNAATCGTTCCCGTATGCCCACCTTGACGATGTCCTTCATATGGACCACGCCGATGGCCCNCGCGCTNCTG

Clone Rv38

:::::::::::Rv38SP6.seq:::::::::::::

Clone Rv390

CTCAAGCTTGCGCTGGATCTGGCGGCTGAGCCTGTTCTTGGGCAACATGCCGAGGGATCGCCTTTTCCACCACGCGGT CGGGGTGGCGTTGCATTAGCTCACCGATGGTGCGCTTGTGCAGGCCGCCGGGATACCCCGAGTGCCGGTAAACCATCT TGTGCTGCAGTTTGTCGCCGCTGATGGCGACCTTGTCGGCGTTGATCACNATGACNAAGTCACCGCCATCGACATTGG GGGCGAACGTCGGCTTGTGCTTGCCGCGCAGCAGGTTGGCCGCCGCGACGGCAAGGCGGCCAANCACCACGTC

#### Clone Rv391

#### Clone Rv392

# Clone Rv393

Clone Rv396

CTCAAGCTTTGTCCGACAAGCGTTCCCGGGCGGTCAGCAAGCGAACGTCGGTTGGCCCACTGCGGGTCGATATTGCCG

WO 99/54487 PCT/IB99/00740

105

 $\tt CGTCAGCACGGCGACGTTACGCCGAGCAGTTACACAATCGCTCTGCAGCAAACCAATATTCTGCGCGACGTTCGAGGAGGACTTCTTGATTGGACTG$ 

Clone Rv39

CCGACGCGCACTACGTGCTGGTGTCCACCCGCGACCCGCACCGGCACGAGCTACGCAGCTACCGCATCGTCGATGGCG
CTGTCACCGAGGAACCTGTCAATGTCGTCGAGCAGTACTGAACCGTTCCGAGAAAGGCCAGCATGAACGTCACCGTAT
CCATTCCGACCATCCTGCGGCCCCACACCGGCGGCCAGAAGAGTGTCTCGGCCAGCGGCGATACCTTGGGTGCCGTCA
TCAGCGACCTGGAGGCCAGCTATTCGGGCATTTCCGAGCGCCTGATGGACCCGTCTTCCCCAGGTAAGTTGCACCGCT
TCGTGAACATCTACGTCAACGACGAAGACGTGCGGTTCTCCCGGCGGCTTGGCCACCGCGATCGCTGACGGTGACTCGG
TCACCATCCTCCCCGCCGTGGCCGGTGGGTGAGCGGACACATGACACGATACGACTCACTGTTGCATGCCTTG

Clone Rv3

TGCTTCCGGCTCGTATGTTGTGGGAATTGTGAGCGGATAACAATTTCACACAGGAAACAGCTATGACCATGATTACG
CCAAGCTATTTAGGTGACACTATAGAATACTCAAGCTTGCCGGGAGGGTGCATGGCCGACTCGGATTTACCCACCAAG
GGGCGCCAACGCGGTGTCCGCGCCGTCGAGCTGAACGTTGCTGCCCGCCTGGAGAACCTGGCGCTGCTGCGCACCCTG
GTCGGCGCCATCGGCACCTTCGAGGACCTGGATTTCGACGCCGTGGCCGACCTGAGGTTGGCGGTGGACGANGTGTGC
ACCCGGTTGATTCGCTCGGCCTTGCCGGATGCCACCCTGCGCCTGGTGGTCGATCCGCGAAAAGACGAAGTTGTGGTG
GAGGCTTCTGCTGCCTGCGACACCCACGACGTGGTGGCACGGCAGCTTTAGCTGGCATTCCT

Clone Rv40

CCTGCTTCCGGCTCGTATGTTGTGTGGAATTGTGAGCGGATAACAATTTCACACAGGAAACAGCTATGACCATGATTA CGCCAAGCTATTTAGGTGACACTATAGAATACTCAAGCTTGTCCTCGGGCGTGGCCTCGGCCAAGAAATCGTCGACGC CGGCCTCCTGTGCAATCGCCTTGGCGGTCGCCGGGTTGTCACCGGTGATCATCACGGTGCGATGCTCATTCGGCGCA TTTCGTCGAAGCGTTCCCGTATGCCCACCTTGACGATGTCCTTCAGATGGACGACGCCGATGGCCCGCGCGCTGCTGT TATCGGTCCATTCCGCAACGACTAGGGGTGTCCCCCCCGCGGAGCTGATGCCGTCAATGGCACCACCTCCTCAG TGGGGTGGCCACCGTGATCGCAAAACCACTTCATCACCGCAGCCGCGCACCTTGCGGATCCGAACGGATGCGCTC

TTCGTTCGATGGCGCCCCCGGCTACGGTTTGACCTGTGGGTGTCGAATTGGGGTCAAATTCCGAGGTCGGCGCGCT
AAGAGTGGTCATCCTGCACCGCCGGGGGCCGAACTGCGCCGGCTCACACCCGCGCAACACCGACCAGCTGCTGTTCGA
CGGCCTGCCCTGGGTATCCCGCGGCATGACGAGCACGACGAATTCGCCGAGCTGCTGCTTCCCGCGGTGCGGAAGT
GCTGTTGCTGTCGGACCTGTTGACTGAGGCACTACATCACAGCGGGGCCCCCCCATGCAGGGGATCGCCGCTGCCGT
CGACGCACCGCGGCTGGGACTGCCGCTGGCGCAAGAACTTTCGGCCTACCTGCGTATCTCGACCCAAGCANGTTGGCG
CATGTGCTGACGCCGGCATGACTTCAACGAACTCCCNTCCGACACGCCGAACGAAGTGTCGTTGGTGTTTGCGTATGC

Clone Rv412

 ${\tt GCGGCGAGTGTGGTGGGTGCCGAACACGAATCCAACGACGCACTGGCGGAGAGATACCACTTGCTGTACTGGAAGCACGTGGTGATGATCTCCCGTGGAATGTGCCTCGCCGCCGTCTATCGAAAACAGTGAGCATGCTGCG$ 

CAACCGCGCTCGGCGCGTCTGGGCCTTCCGCCGGCTCCGCCGACAATTCTATCTCTGGATCAGCGGGGCTCTCCGGGCCCGCCTCCGGCCAACCTCAACAGGCCGCGCCTTCCGGCCGAAACATTCCCTAGCCATATATGATCGCACCTCGATACACGATCTCGGCGCCAACCCCCCAACCTCCGCAATTCAGGTATCCGGG

#### Clone Rv413

GAAGGTCGGCGAAGGTGTGGCTGGNTGCCGATCACGAATCCAATGATGCAGTGGTCGGAAGATATTAGCCACTTGCTG TTCTGGAGACAGGTGCTGATGATCTCCCGTGGAATGTCCCTCGACTCCGTCTATCGAAATCTGTGAACA

to an order to the confidence of the control of the

### Clone Rv414

AGCTTTACGCTGGCGTATCAGCGTTGGGGCCGCTGCCATTTCGGTCGCCCAACGCGTTGCCAGCTCCCTGCGCTGTCAGGCTTGCGCGCCAAACTGGCCACCGCAACAAACTTGGCTGAGCTTGATC

 $\tt CTCTATCTGGCGTCACATTCGCAATCTTTAGATTGCAGATATCGATAAAATCACCCGCGCGACAAGACCGCCATGTCATCTTTCGATGTTATTTCGCCGGCCTGGGGAAAGCGCAACGACGTTGCCTACACGTTCCGCCGT$ 

### Clone Rv415

AGCTTTNCCTTGCATCTGCACCCCGATCCACGTCAGCCACGTCGGCGTTCTCCACCAAGAAGTTGCGGGCATTCTCCT
TGCCCTGGCCGAGCTGCTCGCCCTCGTAGGTGAACCAGGCACCCGACTTGCGGATGAGGCCCTGATCCACACCCATGT
CGATCAGCGAGCCCTCCCTGCTGATTCCCTTGCCGTAGAGGATGTCGAACTCGGCCTGCTTGAAGGGGGGCGAACAGT
TGTGCACGACAACCCCTTCGGCGACGAGGGTGTGCAGTTCCTCGACCTCGAGGTCGAACGTTCGTGCCCGCCGCTTG
GCAGCACTTCTCGGATCACGGAATAGCGGANTTCTTCCGCCAGCATGTCGTGCAGGAATTTGTCATCCAGGGCATCCG
CGAGCGCCTGCACGCG

ACTGTCNAGGGAATGCTTCGCAGCATCTACCTGCAGTCGCTTGTGCATAAGCGGACGGCCCNACCTGTTCGTGTTCCGGGACACCAGACGCGGGAGCACCGGCAGTACGGCGAAAGGTTTGAGCGGAAGGAGTTGCGCAAATCGGGGCGCCCCAACACCCGTCCGCAAGACGCGGTCAACGACCTGTTTCAGGCGATCAGGGTCACCGACTCACCTGCACTGAGAACAAGCGATCTGCTGATCTGCCAGAAGATGAATGTCCACGGCAAGCCTGATGGCCTGCCGCTCTTCCGGGAATGTTTGGC

# Clone Rv416

TGAATTATGATCCCGACACACTGCATCANTTTAGCCGCGTCGNGATGCTATCCGCCGACGGTTTGGANCNGGTCCGT GTCGTTCGTGTTGATCTCACCCGAAGTTGTGTCCGCCGCCGCCGGGGATCTAGCGAACGTGGGATCGACAATCAGCGC CGCCAACAAGGCGGCAGCGGCTGCGACCACGCAGGTGCTGGCCGCGGGCGCCGATNAGGTGTCAGCGCGCATCGCGGC GCTGTTTGGTATGTACGGCCTGNAATATCCGGCGATCAGTGCGCAAGTTGCCGCGTATCACCANCAGTCCGTGCAG

Clone Rv417

AGCTTTGGAGCCNCNCCGANCCNCCGGTACGCCCGCCACCGCCACCGCCACCGCACCCCTTTGAGCCGTTCGCC
GTGGCCGCGGTGGANCTGGCCGACGACGACGACTGATCGTCTGGCCAAAGTGGTCGATGGCACGCTGGCCGCCGATCTG
AAGGTCGGCATGGAGATGGAGCTGACGACCATGCCGCTGTTCGCCGACNACGACGGTGTGCAGCGCATCGTCTACGCG
TGGCGGATCCCATCGCGCGCCGCGACNATGCANAGCGCANCGATGCTGAGGAGCGCCCCGATGAGGATGAGCGCGC
CGGAACCCGTTTACNTCCTGGGTGCCGGTATGCACCCGTGGGGGAAATGGGGTAATGACTTC

TTCTCNCATCGTTCGTACTNNGATGGGACGCTGCTGCCCGAGGCGATCCTGGCCAACCGGCTCTCGCCGGCGCTGACC
TTCGGCGGGGCGAACCTGAACTTCTTTCCGATGGGCGCTTGGGCCAAACGTACCGGGGCTATCTTCATTCGGCGTCAG
ACGAAAGATATTCCCGTCTACCGCTTCGTATTACGTGCTTACGCCGCGCAGCTGGTGCAAAACCATGTCAACCTCACC
TGGTCGATCGAAGGGGGTCGGACCAGAACGGGCAAGCTACGGCCACCGGTGTTCGGGATCCTGCGTTACATCACCGAT
GCGGTCGACGAAATCGACGGTCCCGAAGTGTATTTGGTGCCGACCTCGATCGTGTACGAACAGCTGCACGAAGTGGAA
GCCATGACCACCGAAGCCTATGGCGCCGTGAA

Clone Rv418

Clone Rv419

::::::::::Rv419SP6.seq::::::::::::

AAAGCCACGGAAACGATTGCCTACTGCCGAATCGGGGAACGGTCCTCGCACACCTGGTTCGTGTTGCGGGAATTACTC
GGACACCAAAACGTCAAGAACTACGACGGCAGTTGGACAGAATACGGCTCCCTGGTGGGCGCCCCGATCGAGTTGGGA
AACTGATATGTGCTCTGGACCCAAGCAAGGACTGACATTGCCGGCCAGCGTCTACCTGGAAAAA

TTTCGCCACCGCNAGGTCGTGCGCGTTCCAGAAAAGCGTGGTTTCGCCGGGCGCGAGGATTCGACGGTCCAACTGACC AGCCGGTCCACCCGCTTAGGCAGGATCGCGGTGTCTATATGTTCGCCCTCGGCATAAACGCCATTGCTGCGGTGA AAATCGGACATCTCGCCGATTGCCACGTCTACATGATCCGCTTTGTCCCGCGCCGGGTCGTTGACAAACGCGATGTCN GCCTCCTGGGAAGCGGTGGC

Clone Rv41

GTACCGTCACCATGATCGCCCCCATCGGCATCGGTGAGCTGATAGATCCCAGCCGGTTTCGCCAACCCCGGAGCGATC
TTGGCGCGCTGCTNGTNGTCNCTGANACNTAGCCACCAACAGAGCCCGGTGTGCGACAAGANGACTGATCGGATCTCT
CCGGACACNTCGAGGGGGTCNTCAGGAGNCCGGGCGCCCACCCCGAGGTAAGCCTCCGCCCAGCCTCACACCGCGACCG
GGTATCNCAAGTCGCGCAATAANCCCACCACCTCCTCGGACCCCACGTTGTATGCGGCTGGGT

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Clone Rv42

ATACTCAAGCTTAGACCTCACTGATGTGGCGGGACGCGGGAGATAACCGCGGTTCGAGCCGTTCAACAGTGGTGGTTC CCACACCAGTTGTTTGCCTTTGCGAAGTAAAGCGATTCGATTTGCTCGAAAAGAGGGCTGCTCGTGAGGGACAT CCATGGCCGATACCTCAGCGATCTCAACGGTCAAGCGACTGCATGTTTGGCGCAAGGTATCGCTAAGCATAGGTTCGT GACGGATTTGACAGCAAGAGCTTTCCAAAGATTGCTGTCCACATANTGATTCGCATCTCTACACCTCTTCGCCGGTGC TGTCAAGAGCCATTCGAATCAGTTATCTCGCTGTGCTTGGAAAAATTTTCCCAGCCTGCGTTGGACAAACCGCGTC GCCAAAGCGGT

Clone Rv43

CGGCCGGGATGTGCGCAATGGCAGGTTGTCGCCCGGCTTGATGTCGGCGTTAGCGCCGGATTCCACCACATCCCCTTG
CGAAAGTCCGTTGGGTGCAATGATGTANCGCTTCTCCCCATCGAGATAGTGGAGCAACGCAATCCGTGCGGTACGGTT
CGGGTCGTACTCGATGTGCGCGACCTTGGCGTTGACACCATCTTTGTCATGGCGCGCAAAGTCGATCATCCGGTAAGC
GCGCTTATGACCGCCGCCTTTGTGCCNGGTGGTAATCCGGCCATGCGCGTTCCACCGCGACCGTGCAGCGGGCG
CACCAGCGACNTCTCCGGGGTTGACCGGGTGATCTCGGCGAAATCAGATACGCTGGCGCCGCGACGACCAGGCGTCGT
GGGCTTGTACTTGCGAATTGCCATGGTCTAATCAGGTCTTTCTCTCACCTCTCGCCGGGCTAGGGCGCATTGCCT
GCTCCT

Clone Rv44

CCATTGGTCGGTGTGCGCATACCANTACNACGCGCCGGGCACCTGACGCGGCGGCGCGCAACCATTCGGTGGCCATCGC CATCGTCTGCCACCCGGTCAACGGACGCACCTTCTCCTGGCCGACCTAGTGCGCCCACCCGCCGCCGCTTGCGTCCCAT CGATCCGGTCAACATGAGCAGCGCCAACACCGAGCGGTACATGACATCTGCTGTGGAACCAGTGACANATTCCGCCGC CCATGATGATCNTCGACCGTCCTCCGGATTCGGTC

GCCGGCCTGGTCAAAGGGGCGTCCGAAGGANCCGGGCTGGGTAACAAGTTCCTGGCTCATATCCGCGAATGCGACGCC
ATTTGTCAGGTGGTGCGGGTGTTCGTCGACGACNACGTGACTCATGTCACCGGACGGGTCGATCCCCAGTCCGACATT
GAGGTCGTCGAGACCGAGCTGATCCTGGCAGATCTGCAAACCCTGGAGCGGCCACGGGCCGGCTGGAGAANGAAGCN
CGCACCAACAAGGCGCGCAAGCCGGTCTACGACCCGGC

Clone Rv45

GATCCACTGACCACGATGACATATCGAAATGCTCGACGATTCCGATGGCGATCAAGGCCACGATGCCCTGGCCGTTGGGCGGTATCTGGTGGATGGTGTGATCCTGGTGGATGGTGTACCCGCGGTAGGTTCCCGTGATCGTGTCGACCCAGTCCACGCGATGGGCGGAGGTCGTCGGCACGCATCACCCCGCGTNTGCCGCCGAGTGCGCCTCGAGTTTGGCGGCCAGCTCTCCCCGGTAGAACTCTCACCGTTGGTCGCCGCGATCTTCTCTANCGTCGCCGCGTGGTCAGGAAAGGTAAACAGCTCACCGGGTTTCGGCGCTCGTCGCCGGGCATGAACGCAACGGACCTGTGCCG

WO 99/54487 PCT/IB99/00740

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GAATGGCATGCCCTGGGCCGGGCGTTCCTTCCGCTGCCGGACTCCTCCCACCAATTCACCGCCGAAGGCGTCCCGTCT

Clone Rv46

 $\textbf{ATACTCAAGCTTCTGTCACCGAAATCCCGCATGGGATAACGGGTTTAGATTTCGACAACGGGACCGTGTTTCTCAACAACGGGTCATCAGCTGGGCCGGCGACAACGGTATCTACTTCACCCGCTTTCGCCCGT$ 

:::::::::::Rv46T7.seq:::::::::::::

Clone Rv47

 $\tt CCGCCTCCGCATTATGGGTCAAGAACCATCGGGTCGGACTTCTGGGCTTCCAACGCTCGCGCCGTCCCN$ 

Clone Rv48

Clone Rv49

WO 99/54487 PCT/IB99/00740

110

Clone Rv4

Clone Rv50

::::::::::Rv50SP6.seq:::::::::::

AGCTTCCGTCACGACCCGCCCTCGCCGGTGCCGGCGCCATCGGTCATCGGATCTCATGACGACGTCACGTAGGCCCGC
TAGCCGCGAGCGGGCGGCGGCGACCGGCGGAGCGGGCGACCGGTCACTGGCCGGGCGAGCTGGACCGGTTCACCGCG
GAACTACCGTTCTCGCTCGACGACTTTCAGCAGCGGGCTTGCAGCGGCCTGGAACGCGGCCACGGTGTTGCTGGTGTG
CGCGCCGACCGGCGCTGGCAAGACGGTGGTCG

Clone Rv51

ACGTTGGCTCTGCCGGAACGTATTTCCAGCGGCACGCATTCGGCGTGGGTGCCGGGCGCCGAGTTGCGTCGCTGGGATCACGCAGCAGTCGCCGGCGGCTGCCGTCGGGCTATGAATTGCACCGAGCCGGAAAATCCNCAC

Clone Rv52

ATACTCAAGCTTGTCGTATTCCGTGGCACTGTCAGACATATGCGCCGCTCCTCCTCATCGCTGCGCTCGGCATCGTCGCCCGGCGGTCATCGTCGCGTCATCGTCGCGAGCCGAACGCGAACGAGAACGTGTTCCATTATTAGGGTGTGAGCACCAATACCAGATTGCTCACCAGGAACTCACCAGCACCCGGGACGGATGTCAGCCACCACCCCCATCTGGGGTGGTAGCGGGGA

CGTTGGTAGCCCGATATGCATAGTGTATCTTACTGAACATGATTTCCATTATGGAGCCCGGGGTGCCGGCAGCGCGAACGTCGCCCGTCAGACGCGGCGCACCGGCTGACCAGGGTGTTGCGGGCGAACATCGGCCCGGCTTCGGATTCCGGTCCGGGTACCGGGCGACCCCACCGCTTCGAGGTA

Clone Rv53

ATACTCAAGCTTGGCCAACTCCTCATCGGACTTGAAGGTGCCGTCCTCGTTGGCGGCCCTGCTCCACGGCACGTTGAT
GGCACCAGGAATGTGTCCGGGCCGCTGGCTTTGTTCCTGCGGCAGGTGCGCGGGGGGCCATGATCTTGCCGGAAAACTC
GTCGGGAGAGCGCACGTCGATGAGGTTCTTGACGTTGATGGCCGCCAGGACCTCGTCGCGGAATGCCCGAATCGTGTT
ATCCGGCGGGGAGGCGGTGTATGAGGTCACCGGCCGGCTGACCGGGTCGCTGGACAGCGGGCGTCCCAGCTCCCA
CTTCTTGCGGGCGCCGCCCACNACTTGACTTCTCCTGG

::::::::::Rv53T7.seq::::::::::

ATATCTTAAGCGTCGGGTCCCGAGGCTCGGTCGGCAGCTCCAGCAAAACCCGCTCCACCCTAGATGCCGGTATCCCT
CAAGGTCTTTAGCCGCCGCTTCACCCCACTGGCACACGGTCACCGGCACGTCGCCCCCGGCCATGGCGCAACCGCT
GAAGCGGACCCGACAGCCGCTGCGGTGATGGACTGATCGCGATCCACCCGGCATTGAGCCGGGCTATCCGCGGGAAGT
TCGCCGGTCCCCCGCCCACATACAGCGGAGGATAGGGCTTTGTCACCGGCTTCGGCCAGCAGTAGATCGGATCGAAGT
CCACATATGTCCCATGGAATTCCGCCTGCTCCTGCGTCCAGATCTCGATTATCGCGCGCAACCGCTCATCGATCACAC
GTCCGCGCACCGCAGGGTCCACACCATGGTTGGCGACTTCTTCGCGCA

### Clone Rv54

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# ::::::::::Rv54T7.seq::::::::::

### Clone Rv55

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CTTCCGGCTCGTATGTTGTGGGAATTGTGAGCGGATAACAATTTCACACAGGAAACAGCTATGACCATGATTACGCC AAGCTATTTAGGTGACACTATAGAATACTCAAGCTTGGCCACCTCGCGGTGTGTGGGAACCCATCTGAGCAGTGTG CCAAACCGGGGCAGACAGCTCCCAATTGACGTGAGCCCGCTCACTTGCTGGGTAAGCGTCG

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#### Clone Rv56

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GCTGAGCTCCACGGCGTGGATCAAGGTACCGGCCGGGATGTTGCGCAATGGCAGGTTGTTGCCCGGCTTGATGTCGGC
GTTAGCGCCGGATTCCACCACATCCCTTGCGAAAGTCCGTTGGGTGCAATGATGTAGCGCTTCTCCCCATCGAGATA
GTGGAGCAACGCAATCCGTGCGGTACGGTTCGGGTCGTACTCGATGTGCGCGACCTTGGCGTTGACACCATCTTTGTC
ATTGCGGCGAAAGTCGATCATCCGGTAAGCGCGCTTATGACCGCCGCCTTTGTGCCGGGTGAATCCGGCCATGCGC
GTTGCGTCCACCGCGACCGTGCAGCGGGCGCACCAGCGACTTCTCCGGGGTTGACCGGGTGATCTCGGCGAAATCAGA
TACGCTGGCGCCGCGACGACCAGGCGTCGTGGGCTTGTACTTGCGAATTGCCATGTCTAATCAGGTCTTTCTCT

Clone Rv57

ATACTCAAGCTTGTTGGTGACCTCGCCGGCGAACAGTTCTCGCACGATTTCCGGATTAGCGGGACTGGTCACCAGTTGGTATGCGGGAAGGCGCTGACGTTCGCCGCGATTAGCTGTTTGATGGACGCGGGGTGATGTCCTGATCACGGAACTGGCTGTAATAGCCCAGGGTCGCCACGCTTCCATCCGGGCCCGGACCCGGC

Clone Rv58

Clone Rv59

:::::::::::Rv59SP6.seq::::::::::::::

NCGTGGACACCGGTGTCGANCGCCACCAGCCGCATGTCTGCANGTCNATTCCGTCCTCGGCAACATCTTGAATGCCGA GCAGCGCCTGGGCGTGATCGGCAACCGGGGATGACCGCTCGCCGATCCGCTCGACAATCCCGGCGGCACGTGACATGC CGGCGGACGGCTCGACGAGCTGGAACTTCAGCGACGACGATCCGGAATTGATCACCAGCACGGTGCTACTCATGGACC CCTGCGCCTGAATCCCGTGATGGCCACGGTGTTGACTATTCGTCGACAGTGCACCCGAGATAGTCTTCACGGCTGCGT

CATGTATTGCCGTGCTCACGGCGCCACGCTCGATGGTTTCTCGAAGTCTCCGGGCTGGTGTACAGCTTCTCGTTGATC
TCGTTCGCCACGCCGTCCTCTTCCCGCCGACGACCCGATCTCGATCTCCANAATGATCTTGGCGGCCGCCGCCGCCTT
GAGCAGCTCCTGGGCGATGGCCAGGTTCTCATCGATGGGCACTGCCGACCGTCCCACATGTGCGACGGAACAAAGATG
TCACCTTGCTCACGCGTGCGCNAGATCNCANAAGGGCCGGACATACTGTCNACTTGTCCTTGGGCAGTGGTCCGTGTC
AGCCCACGTGACGGGTACTTGGCGCGATAACGTGGTG

Clone Rv5

::::::::::Rv5SP6.seq:::::::::::

GCCACCACGACCGGCCGTAACTCTGCTCACGGAAATGCGGCCAGGCCGCGCGTAGCACGTGGTATCCGCCATAAAGG TGCACCTTAAGCACGGCGTCCCAATTCTCGAACGACATCTTGTGGAAGGTGCCGTCGCGCAAGATCCCGGCGTTGCTC ACCACACCGTGCACGGCCCGAATTCGTCAAGCGCGGTCTTGATGATGTTCGCTGCGCCGTCCTCGGTGGCGACGCCTG TCCTTAGTTGGCGACCGCCCGGCCCCCCTTGTCGCGAATCTCGGCGACGACCTCATCGGCCAACGGCGCCC GTGCCCGTCGCGGGCGCCCACCGAGGTCGTTGACCACGA

CAGGCATGCAACCTTTGTCCACACGCGTCTACTCCGTGCAAGGTCCGACCGCTTCCACGTCCCGCGTGACGGTGCTCCCTCAGCAACGCGTGAAGTGGTCCGATCCCGCGCTTCAGG

Clone Rv60

TTNCCGCCTTNACGCCTACTCCNAGACGATGCTCGACGCGTGTGAGCACACGGCGCTGCTGTAGACGGCACGGCGCAG CTGGATCGCGCTTGGTGCACCCAAGCCTCTACGCGCGTCGTCGTCGTCATCGGGTACCGAACATATTCCGGTCGTT GCGCAGAGTGTGCATGTGCGGCTCTTGTGAACGAACATAGCAAAGCGTATATGTCTGTGGCGGCTCTGCAGATATCGC GATAATACGTATATACATAAGGTGGCGCGCGATCTATCGGTATATCCGTTATGGCGGACGTGAGCGTGAGTCGC GGCGCATCGCGCACTTCGCGATCGCGTGACTGGTCCTCGCGACTGCGCGCATGCGTAGC

Clone Rv61

GGTGATGACGCACTTGCTTCGAATGAGTCATTGACTACTCCCGTGGTTGTCCTGCGATGGTGGAGTGCCGCGCAGCCT TGCCCGANGTCGCGATCGCGTCGCGGGCTTCGGGGAGCAGACTGACCTGCAGATGGAAGTCGTGCCACATGCCCGCGA ACGCCGAGCTCGATGCTTGTTTTCGAAGNGCGCANGCGGTTTCGATCTTGTCCGCGTCAACGCAGATCGGATCTCGCC GCGTCTGCATGACGATGGGCGCAGGCCCGCTCATGTCCCGTAGACGGGAGATACGGGCAGCCGCGGATCGAGACCT ACGTAGCGCGGCGCCCCATCGTGCCATCGACGAAGAATGACGGATCGCGCAGCGCCGTCGCTTCGATGTCACGC GAGATCGCCACGGCAGATCAGCGATGCGCGGGC

CGGTACGCCGGCAACAAACGCCTTGTGACGAGCGCGTCCGAGCGGTCATCGGCCTCCACCGTCATGCACAGCTCCTTC
TCCAGGTCTACGCCGACGTCGCGGTCCACATTGGTGAGCTTGGCGAATGCCTCGGCAACCTCGTCGAAATGCGCCTCC
GCGTCCGCATCGAAGGTCGCCATGTCAAAGATCAACTCGACGTAGTAGCTAGTTACCGCATCAGGTCAGTGTTTGCTG
GCCTCGGAGTCCGGCCGAACAATGGCCATTTCCCGCGACTCTAGAATCCAGTCATCGTCTCGGTGACGACGCCTTGCC
GATCACATAGCTCGACCGGATCGGAGAGAATCTGGTTCTCGT

Clone Rv62

GCAAGTCCGCTCAATGTGGTTGTGATCACANGACTACGTCGCCTCAATCAGCTCAAACGTCACCCCGTGGCGTGCTGC GCAGCATGAAGGTCGGCGCCCGCACGATGTGGGCGAAGCAACAGGTAATAACTGGTCGGCATGGGTCAACCCTCATTG GGCCGTTGCGGATCGGGTGCACGCCCGGAGTGCCGGTCGAACTCAACACCGCCTTCACCGATCTTTTCGTCGAAAATG GCGGTCGTGTCGGGGTATACGTCCGCGATCCCACGAGGCGGAATCCGCTGAGCCGCACTGA

Clone Rv63

Clone Rv64

#### Clone Rv65

::::::::::::::Rv65T7.seq::::::::::::

### Clone Rv66

### Clone Rv67

ATACTCAAGCTTATCGAGGCGGCGCATACCGAAGCGTGGGAAATCCAGACCGAATACCGCGACGTGCTGGACACTTTG
GCCGGCGAGCTGCTGGAAAAGGAGACCCTGCACCGACCCGAGCTGGAAAAGCATCTTCGCTGACGTCGAAAAGCGGCCG
CGGCTCACCATGTTCGACAACTTCGGTGGCCGGATCCCGTCGGACAAACCGCCCATCAAGACACCCCGGCGAGCTCGCG
ATCGAACGCGGCGAACCTTGGCCCCAGCCGGTCCCCGAGCCGGCGTTCAAGGCGGCGATTGCGCATGCTACCCAAGCC
GCTGAGGCCGCCCGGTCCGACCCGGCCAAACCGGGCACCAACGGTTCGCCCGGCGCACCACCGGTCCGGTGA
CCGCAGTACGGTCCCCCCAGCCTGACTACCGTGCCCCGGCGGCGCT

Clone Rv68

CACGCGGTCTGGCCCGATCCGAAGATCCCTTTGCCGGCGTGGCGGCTCTGCTCGGCGGTGTTGTACACTTCTCGAACA
CCTCGGCACCGACACCACCACCGTNGCTTGAACACCGCCAACATCGGCAGCAGATCTTGATGGTCCTGGTGAATCCCA
CGGTGACTTTGGAGTGGAAGGCGCCATACTGATCGCCGCGCCAGCACATGAGCTAGCGGCAGGAAAACCAGCAGCCGC
TCACCTTGCGCAGCAGCGTCNGGTGATATGCCTGGCGCCCTTAATCTCGTGAACCAGTTGGATTGGGTCAACTGGCAG
CCTTGGGTCTCCGGTGGTGCCGANGTGTANATAAGCTCCCGGGTCCGTCAACGTANTGCGCAGGCGGCGGTTACTCGG
CGGGTCAACGAGCCCCGCTCGTGAGCNATCAGCCTTTGGACCGAACGGGATTCATACTCCGCAGGCGGCCCTCCGAAA
TCGGCACATGTCCTTTGATCGTTCGCAACAN

Clone Rv69

Clone Rv6

GGGTCTACAACCACCGGGTCTGACTTCTGGGCTTCCACCGCTCGCGCCGTCGCGACAAACAGCGCGGTCGAACCGACA CTCGTTGTGATGTCCCAGCTATCACCTCCGGTAGGCACCCAATCGACCCTACCCGGCTATCTCACCCCGATCTCCAG GCTCCGCCGATCCATGCGCATCCCGGTCCGGATCCC

CAGGCATGCAAGCTTGTCGTATTCCGTGGCACTGTCAGACATATGCGCCGCTCCTCCTCATCGCTGCGCTCGGCATCG
TCGCCGGCGGTCATGGCGTCACCCTACCCAAGCCGAACGCGAAACGAGAACGTGTTCCATTATTAGGGTGTGAGCACC
AATACCAGATTGCTCACCAGGAACTCACGCAGCACCGGGACGGATGTCAGCCACCACGCCCATCTGGGGTGGTAGCGG
GGAAATACGGCTAACGCGGCTCCGGTGCCGGCAGCCCAGCGCAGACCCTCGGCGGCGGACACGGCTAACAACGACGAC
CCATAGTTGTTCTTTGCCGGATGGCCGTGTTTGCTGACATATCGGGCGCGGCGCGCCGCCCCC

Clone Rv70

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::::::::::Rv70T7D3.seq:::::::::::

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TCGACCGCCCCCCCCGAGTTGGGTCATAACGAAGTACTGATGCCGATCATGTCGACGTGTCCGTCGCATCAGCGTGCAG
CGGCGACCCCTCGACGAGCCTCGGTGCCGCCGCGGCCAGGGCACCAGCTGTTTTAGCGCATTGTGCTCCGCCGGTAAT
AAAGGANGTCGGTCGCCTCCGCTGCTGTGGTTGCGGAATAACATCTTCCCTTCCTGCAACAGGATGAGAATGGTTTTA
ATTGCTC

Clone Rv71

 $\verb|CTAAGCTTTCGGGTCCGCCGCCACTAGTACCGCGTTGCCGGCCCGCCGACCTAGAATGTTCCGCCCATTGCCGTTTC| \\ \verb|CTCCCGCCGCCGCGGGTT| \\ |$ 

::::::::::Rv71T7.seq::::::::::::

TCTGGTGCCGGGTGTGCCGACGGGTCCGTCCGCCTCTGCTTCAGTGATTCTGTGATGCGACCGGCAACGTCCTCGTTG
TTCGGTGTCTATGTGGTCCGTCTCTCCTTGTTCCGCATACGATT

Clone Rv72

GCGATCGNTNACCACAAGGGCGCAACCGTTCGCGCGTCGACTGAACGTGCTGCCGCCTGGAGAACTGGCGCTGCTGCCACCTGGTCGGCGCACCTTCGAGGACTTCGAGGACTTCGACGCTTCGACGCTGGACCTGANGTNGGCGGTGGACNNGTGTGCCCCGGTTGATTCCTCGGCCTTGCCGGGATGCCACCTGCGCCTGGTGGTCGAT

CGTGACCGGACGGGTGCCGCGCAACCGGTCTTGGCCAATTGCCGGGGACTGGGGCTGGAGTATAAAGCGGGCCTGT
TGCCGGAAGATAAAGTCAAAGCGGTGACCGAGCTGAATCAACATGCGCCGCTGGCGATGGTCGGTGACGGTATTAACG
ACCGCCAGCGATGAAAGCTGCCGCCATCGGGATTGCAATGGGTAGCGGCACAGACTGGCGCTGGAAACCGCCGACGCA
CATTAACCATAACCACCTGCGCGGCTGGTGCAAATGATTGAACTGGCACGNCCACTCACGCCAATATCCGCCAGAACA
TCACTATTGCGCTGGG

Clone Rv73

:::::::::Rv73SP6.seq:::::::::::

Clone Rv74

TCAGCTGTCTGTAGAAGGGCTGGCGATACTGTGCACTGTCTGATATCGCNNCGTNGTGGGACTATNCAGNCCATNANG ATGCGGTTCNGNNNNTGCAGAGNATCCTGGNACACATNCGGTTCACGTTAATCANCATCGCGANTTNCTNCGTNTTCG ATTANTTCTGCTAACGNNTCTNNNAGTGCCTGCGGGTCGACTCTAGAG

Clone Rv75

NCTCTGCCGGGCNAGAGCGCAGAGTCGGACGGCTTCGTCGATCGTGAAGCGACCNTGCGATGANCAGATATCGNTNAC ACTGCTCANAAACTTCGGATCATCGNTGATACACAGGCCAACGGGTAGCGGTTGTCCAACCGCTTCGTCAACGANATGGGATCGTGACGANCCTACGCTCGCAGGATATGTCGCNGACCNGNTCTAGANAN

::::::::::Rv75T7D3.seq:::::::::::

 ${\tt CACTTCATGCTCGTGCGTTGGCNTCGATTTGCNCGAGNGGTTAGCTCCTCGAGTGNGTGACGTATCACTCCGGCNGACTANCCGTATCNGCGTCCCGCACCGGTCAACTGGTCTAGCCACCCGGGGGAGAATNCNCGACCGGNGCTATCGACCNATCACGGCTTGTCGNNAAGATAGNCAGCC$ 

Clone Rv76

::::::::::Rv76T7.seq:::::::::::

CGGTCGGTGTGCTTGGCGGCGTCGGTATCAACACCGCCCACGAAATGGGGCACAAGAAGGATTCGCTGGAGCGGTGGC TGTCCAAGATCACCCTCGCCCAGACCTGCTACGGGCACTTCTACATCGAGCACAACCGTGGCCATCACGTCCGGGTGT CCACACCGGAAGACCCGGCGTCGGCGCGGTTCGGCAAAACTTTGTGGGATTTCCCGCCCCCCC

Clone Rv77

::::::::::Rv77SP6.seq:::::::::::

:::::::::Rv77T7.seq:::::::::::

GATGGCACTCACGCTGGACAAGACCTTCACAAAATCTGAAATCCTGACCCGATACTTGAACCTGGTCTCGTTCGGCAA TAACTCGTTCGGCGTGCAGGACGCGGCGCAAACGTACTTCGGCATCAACGCGTCCGACCTGAAATTGGCAGCAAACCG GCGCTGCTGGGCCGGGCATGGTGCAATCCGAACAAGCACGCTCAACCCGTACACCCAACCCCGAAGGGCCGCTGGCCCG GCGGAACCTTGTCCTCCA

Clone Rv78

AACAGCTATGACCATGATTACGCCAAGCTATTTAGGTGACACTATAGAATACTCAAGCTTCTGGGCGTCGTGGTGCCC
GGCCTGCCGGTGCAGGAACTGGATTTTACTGCCATCTCTCGCGACCCTGAGGTGGTCCAGGCTTACAACACCGACCCA
CTCGTGCACCACGGACGGGTTCCGGCCGGGATTGGCCGCGCGCTGCTGCANGTGGGCGAGACCATGCCGCGGCGANCA
CCGGCATTGACCGCCGCCTGCTAGTGCTGCACGGCACCGATGACCGCTGATCCCCATCGAAGGCAGCCGTCGCTG
GTCNAATGTNTNGGATCNGCCGACGTGCANCTGAANGANTATCCCCGGCTGTNCCACNAGGTGTTCAACGAACCGAN
CGCAACCAAGTG

CAAGGCATACGCCAAGACCCAAGGGATCGCAGTCACCTCCGTCAACGGCCTGGTCGCCGGCCACGGGTCCGTGCAGGA
GACGTGGCTGGCCATGCAAAGCGCCGCCGCCTTATCAGGAACGCCCCGGCTTGTCGGCTTTTCCTGCATCGACACATT
TCCGGAGGTGTTGTGGTTGGCGCANCGCGCGAGACAGGCCTGGGATGGCGTGCGCATCGTCATCGGGAATGCGATGGC
AACACTGAACTACGAGCGCATCCTGCGCCAGCATGACTGTTTCGACTACGTCGTCGTTGGCGACGGGGANGTAGCGTT
CACCAAGCTGGCCTTGGCCCTGGCGAATGACCTGCGGTTGACGACTCCCGGGGACTAACCCGCCGTANTGAGCAAGGAC
AGATTCTGCGCACACCCTCCTCGCTGGTCGACCTTGACA

Clone Rv79

AACAGCTATGACCATGATTACGCCAAGCTATTTAGGTGACACTATAGAATACTCAAGCTTGCCGGTGATCTGGGTGGCCAACTCGGCGGGCACCATCTCCATCACGACNGCAAACGCTCCGGCTTCGGCGACAGCGATCGCGTCTGCGATNGTTTGTTCGGCGGCGTCTCCGCGGCCCCTGCACCCGGAAGCCGCCCAAGGTGTTGACNCTTTGCGGGGGTGAAGCCGATGTGTGCCATCACCGGGATNCCCGCCGCGGTCAGACANGCGATTTGCTCGGCCACCCGCTCACCGCCCTCGANCTTGACNGCATGTGCCGCCCCCCCCTTTGAAGAAACCGGTGGCGGNGGCAACCC

Clone Rv7

:::::::::Rv7SP6.seq:::::::::::

Clone Rv80

Clone Rv81

AACAGCTATGACCATGATTACGCCAAGCTATTTAGGTGACACTATAGAATACTCAAGCTTGGAAAGGAGATCCCCGGG
AACCTGGTGGCAACCCCGCCATTGGGGTTGTTGGGATTGCCGATCAGCGTGAANGAAAGCTCGTCTGGAGACAGCGGG
TCGGCCGAAGCCGCAAGATTGGCCATCACTAGTGACGANATCGTGGCGCTCTGCGAGTANCCNAAGACAGTGACGTTG
TTNCCGGCGGCAATTTGCTGCCGAATCGCACTTTCGAGAATGACNGCACCCTGCGCCACCGANGAATCNAAAGTGAGG
TTCTTGATCACGACCACCGGGTNGAGCCCTTGGGGCGTGAAGANCGCCTGCGCNATAACACCCGGGACGCTGCCACTC
ATGTNCAGCGCGTTCGCGANCTCNACATATCT

Clone Rv82

AACAGCTATGACCATGATTACGCCAAGCTATTTAGGTGACACTATAGAATACTCAAGATCTGGTACCCATCCGTGATA
CATTGAGGCTGTTCCCTGGGGGTCGTTACCTTCCACGAGCAAAACACGTAGCCCCTTCAGAGCCAGATCCTGAGCAAG
ATGAACAGAAACTGAGGTTTTGTAAACGCCACCTTTATGGGCAGCAACCCCGATCACCGGTGGAAATACGTCTTCAGC
ACGTCGCAATCGCGTACCAAACACATCACGCATATGATTAATTTGTTCAATTGTATAACCAACACGTTGCTCAACCC

TCCTCGAATTTCCATATCCGGGTGCGGTAGTCGCCCTGCTTTCTCGGCATCTCTGATAGCCTGAGAAAAACCCCAAC
TAAATCCGCTGCTTCACCTATTCTCCAGCGCCGGGTTATTTTCCTCGCTTCCGGGCTGTCATCATTAAACTGTGCAA

### Clone Rv83

AACAGCTATGACCATGATTACGCCAAGCTATTTAGGTGACACTATAGAATACTCAAGCTTANCGCCACCTCCCGGGCG GAACTCCACGGCGTGGATNAAGGTACCGGCCGGGATGTTGCGCAATGGCAGGTTGTTGCCCGGCTTGANGTCCGCGTTAGCGCCGGATTCCACCACACCCCTTGCGAAANTCCGTTGGGTNCNATGATGTNNCGCTTCTCCCCNTCNANATAATGGANCAACGCNATCCGTGCGGTACGGTTCGGGTCNTACTCCATGTNCGCGACCTTGGCGTTGANACCATCTTTGTCATTGCGGCGAAAGTCNATCATCCGGTNAGCNCGCNTATGANCGCCGCCTTTGTGCCGGGTGGTAATCCGGCCATGCGCNTTGCCTCACCGCGAACGTGCAACGGGGCCCCAACGANTTCTCCNGGGTTGAACCGGTNATCT

#### Clone Rv84

AACAGCTATGACCATGATTACGCCAAGCTATTTAGGTGACACTATANAATACTCAAGCTTGCGGGTNATNGCCTTGGTCAACGGCACCGTGATCGGATCNGGGTCTACCGCACACATNGACTGGAGCTTCGGCGAANTCATCGCCTATGCCTCGCGGGGGGTGACGCTGANCCCNGGTGACNTGTTCNGCTCNGGCACGGTGCCCACCTGCACGCTCNTCNAACACCTCANGCCACCGGAATCATTCCCNGGCTGCACGANAGCGANNTTGTCNCCCTCCAAGTCTAAAGGCTGGGCGANANAAGCANAACGTCCCGACNAACGGCACTCCTTTTCCNTTTGCTCTTC

### Clone Rv85

# Clone Rv86

GATCTCTGGATCGGCGGGGCTCTCCGGGCCGGCCTCGGCGACCTCAGCGGGCCGCCCTTCCGGCCGAACCATTCCCT
AGCCATAGATGACCGCACCTCGATGCACGGTTTGGCGGCAACGCGGCAAGGCGTCNGTCGGGCCCAGCCGCGCAATG
CGGGTACCCGGGAGCGCGGGTCNGTANACCANCGCTGGACTGCGTCGCGCGGTGCGTCNACNTCAAAGTCCCCGGCGT
CCCATATCGCGTATGACGCGGGCGCCCCGGCACCANGGGTGCCGATCCGGCCGTCTCGAACACCACCGGCCCCCAG
CCGCCGCGGGTCCGGCAGCNAACCCGCCCGCGCGCATACCCGCTGCCGTGCTGATTGACCGCCGCGCGCACGCT
GGCCANGGATCAAAGCCCGTG

### Clone Rv87

### Clone Rv88

GTCTTTCGATGCTGCTTCTTCGGCGCTGACGCTGGCGATCTATCACCCCCAGCAGTTCGTCTACGCGGGAGCGATGT CGGCCTGTTGGACCCCTCCAGGCGATGGGTCCCACCCTGATCGGCCTGGCGGATGGGTGACGCTGCGGCTACAAGG CCTCCGACATGTGGGGCCCGAAGGAGGACCCGGCGTGGCAGCGCAACGACCCGCTGTTGAACGTCNGGAANCTGATCG CCAACNACACCCNCGTCTGGGTGTACTGCGGCAACNGCAAGCCGTCGGATCTGGGTGGCAACAACCTGCCGGCCAAGT TCCTCGAGGGCTTCGTGCGGACCATCAACATCAAGTTCCAAGACGCCTACAACGCCNGTGGCGGCCACAACCGCGTGT TCGACTTCCCGG

GCCAGGTCGAGGTCCCATGCGCGTGGGCCATTGATGCTGATCGCCAGGACGTCAAANATTTGGTCCGGCGTCAGCTGGGCGAAAAACGTGGGCCCCAGGACTTGCCCGGAGCTGCCCGGGTTCCCGTCGCGCAGCTCGGCGCCCCGGTCAGAAAN AAATTGCGCCAGGTCGCACACTCCGCGCCGTANGCCAGCTGCTCCAGGGTGTCGGCATAGAGCCCGCGGGCCGCAGCGTGCTCGCTGTCGGCGAACACCGCATGGTCGAGAAGCGTTGCCGCCCAACGGAAATCACCTGCGTCNAANGCTTCGCGGGCCAACTCCAGCACTCGGTCGATG

#### Clone Rv89

NAAACGTTCCGGCTTNGGTGCCGGGCGCTTATTTGCGTCTCTGGGATCACNCTCAGTCGCCGGCGGCTGCCGTTGGGC
TATNANTTGCACCGANCCGGAAAATCCGCACNANAACTGCNAGTAGCGGCCTGCAGAANTGCATCCTCGGCGAANCNG
ACTACCGGTGGACANCNACAAGCGCCGCCGAACAACGCACTGGCCCGAGGGATNGGCGTCTATCGGCCCCGCCCGTCG
AACTNGGAACAGACNGTGCGGTTCTACCGTGATCTGGTGGGAATGCTCNACCANACCTTCCCNANNGCTACGGAACNA
CGGCGCGATATTCNGCCNTCCCANCTCGAGCCTGACNCTNGATATCGTCGANNCTCACCATCNCGATCNGCTGTGCCG
GTNTTGCTCGGACTN

CGAACGACGACNCCNCAAGCCATGGTGGTTGGCGCCGTCAAAAGGTCCGCGGTCGCCACTACTGGAAAATCGCCTTG
AGCGTCNCTCGACCNCCGCCTCGAGTTGGGTCNTAACGAAATACCTGATGCCGATCANGTCNACGTCTCCGTCGCNNC
AACGTGCAGCGGCGACCCACTCTACNANGTCTCGGTNCCGCCNCGGCCAGNGCACCACCAGTGACNAATCCNTGCGCC
NTCGGGCCNAGCANTCCCGGTGCNACCGNGGTGGGTCCGGCGATGGTNGGGTGTNCTCNNTACNGGAACGCCAGCGCN
ATCANCATCGGCANACTCNCGTCGATGTGCCGCGGCGCAACCATCCCCCCACAATGATCNGGTGCGTCTGATCAGGCN

Clone Rv8

 ${\tt TTAGGCGTGACGGCCACCGGGGCCACTCCGCACAATCTGTACCCGACCAAGATCTACACCATCGAATACGACGGCGTCGCGACTTTCCGCGGTACCCGCTCAACTTTGTGTCGACCCTCAACGCCATTGCCGGC}$ 

::::::::::Rv8T7D4.seq::::::::::

Clone Rv90

CTTTTCNCGATGTCTCATGATNCCNANGGAGAACNNTGCNANCNCNGCCGCTGACNTNGCNCACCGCTNTGGCNGNGG TGACATTGGTGGTGGTTGCGGGCTGCNACGCCCGACTCGANGCCGANCCATNTNTTGCGGCCGACCGCNTNTCGTCTC NACCGCANNCCCNATCTCNGCCGCNCCCGGTGGANCTACNGCTNCTTCGCCATCTCTCGCCNATGGCTCCNGCGNNTC GCNCAACGTNTGGTTTGGTNANCTGCCTACCTGGTCNT

GCTGCGCCAGTCGTTCGGTGCGGTCATGCCGTTGGACCNACCATCGGAGTTAGTTGCCGAACCGCGGACCACCGCAAGCACCGCGCGTCGTGGCGGACCACCGCAAGCCCGCAGCCCTTGGTCGCGCACCGCACCACCACCACGCCGCAGCCCTCGCCGCACCAATCCACCCGCTTGGCGTCNAANCTGTNGCATCGGTCGGTGACAGCGCCGACCACTTGGACAGCGCGATGGCGGTGAACGGTNANTAGGTGACCTGCCNCCGCCCGCCAATGCCCACCTCCGCTTCACNCATGCGAATGGTCTGACACGCCNAGTGAATTGCCACCAGCGACAACAAAAATCGGTATCTNCNGCGACGGCGGACACGCNATCCCNACTGATACTCGATCCGCCCACCGCTTGNANCTCCGGGTTCCNGTGCTCATGTACCNTCATGTCGGTCTGCGCNCGATATTGACGATCGTGTTTCCCACCGANNANAGANCCTCATCACGCCGGTTCCAGTGCCG

Clone Rv91

CTGTGTGCGGNCGCCGCGATATCGGCCTTTTTACTAACCGAACCCGATGTGGGCTCCGATCCGGCGCGCATGGCATCT ACNGCGACGCCGATCGATGACGGCTTACGAGCTTGAGGGTGTGAANTTGTGGACCNCCAACGGTGTGGTAGCG GACCTGCTANTGGTTATGGCGCGGGGTACCGCGCAGTGAANGGCACCGAGGGGGAATCANCGCCTTTGTCGTCTANGCT GATTCTCCCGGGGATCACCNTGGAGCGCNCCNCNANTTCATGGGACTGCGTGGCATCCAANACGGCGTGACCGGCTTCA TCCNTCNGGGTGCCCAAAGACAACTTGATCNGCNNGGAAGCGACGTCTGAANATCGCGCTGATCNCACTCAACGCCGG ACGCTGTCCTACCGGCGATCGCACCGGANTTGCCAANCCGCGCTNANNATNCGCGNGAATGNCCGTCCACNANTGCAT GG

Clone Rv92

NGGCNGGGAAGTTAATGCCCTACTGGTTCNATGCTCNCACNTCNCCNGTGACNNCCTGCNCCGACCCGCGAGGTCCT
GNCCGTNACCACCGANCNGGCGATCCGGGACTCTNGTACGCATCCAACANNGANCAACGTGCACGGGCGGAGTNGTNC
CGCCACTTCGNCNATGACGGGGTCGATCCNTTCGACGTCCGTCGCCGCGTCGGTCGAGTGGCGGTCACNCTCCNNGTA
CTCGACCNCACNGACGAGAGGACTCGANCCCATCTACGTGTGGACGAAACANATCTTCTGTCCNACGACTACACCACC
ACCCAGGCCATCGCCGNCGCCCGCGANGCCCCTTCGACGCCNTACTGGTCCNGNGGNGGCGCTCTCCGGTTGTCTNNC
NCNTGNCGTGTTCCTTCACNCACTGCCCNACATCGANCCCGAGCNATNCNANGTCCGTCAATC

GGACACTGTTCGCGTGCCCCTCGTCAAAGCCGGAGTGGTCGTGCTGCGCCGGACCCGACCCGACCCTTCAGCGGGGGTT CACAGCTCCGTGGGTGCCGTTACTTCCGATCGCCGCAGTGTGCGCGTGCCTGTGGCTGATGCTGAACCTCACCGCGTT GACTTGGATCCGGTTCGGGATCTGGCTGGTGGCCGGAACCGCGATTTATGTCNGCTACGGGCGCCGCACTCGGCGCA TGGCCTTCGGCAAGCNCNANANAACGCGACCCGGAGGTGTTGAACTAGCTTCGCCGCGTATTTACAAATTGCNTTATA TGTCTACACATAAGACGCAAACTGCTCTATTGTCAANTCCCANCGTGGTGTGGCNCATGAAGATGTTTTGG

Clone Rv94

::::::::::Rv94SP6.seq:::::::::::

TCCTTCTCGGTATCGGTTTGGGCTGTCACCANCAGTTGGTAGTTCTTCACGTNCTGTTGTTCGAGCGTCNAGCCGTCGCGGCGTGTCNANGTCNCCGGACGCGTCACCAGCCGGTCANGGTGCCCTTCCANTCCACGCCGCTGTGGTCGGCGACGCTNATCTTCAATCGAGACCATCGCCAGCTTCATCNTGTTGGCGATCTTGTCNNACGGCACCTCNAACCGGCGCTNCTAGTACNCCACNCNATCNTGTTNCCTTCNCGTCNACATCCTCGATNCCNCNTGCACTTTCCCTCGANCNCCTGGGCCGAGCCGTTGGCANTNACCTCNGAGCCCCATTGGACATCANCCCGCCTGCGAACGGGAACGTCAGCNCNCTGGCCGACAACCTGGCCAACAN

CACNCCGTGATCGCNAGCCCCNGTAGAAATNGTTGAGCCAGTTGGTGCGGCGCTCGTTGCCGGCGGTNATCTCGTCGAGCTCNTCTTCCATCGCCGCGGTGAAGTCGTACTCGACNAGCCGACCNAAATGCTGCTCNAGCAGACCGGTTACCNNNAACNCCNCCTCNTGACNGCACCAGTGCNCTGCCCTTCTTGTGCACGTACCCGCNATCCTGGATGGTCTTGATGATCNACTANTNTGTCGACGGGCGGCCGATGCCCATCTCCTCNAGCGCTTTGACCAGCGACNCCTCGGTGTATCGGGCCGGCGGGTTNGTGGCATGGCCGTCTCACNACNATNTTCANCCGTTGACCCGGGGTCACA

...

Clone Rv95

:::::::::::Rv95SP6.seq::::::::::

TGGCCTTCTTGNCANGGGCNNACATNNGCTATNGCGAGCGTGTAACCGATCATCNTCCNGGCGACTGTGGCCTGANCGGCAAGGGTNGCCTNATTCNTCCTCCTGNGGCATGGTTNCCACACGGAATGNCGGTAAGTCTGGTCGGCAACCTGGCCCGCTGCGGGTTGGGTTCGGATTCGCTCGGCTANTAAGGTGCTCGCCTGGTGTNACNACTAATCNCNATATACNCTTANCGGAGTNGNCGTCCCGATCCTNGCCCTGCCGCNGGCGATCNCGTTCGCANCACCGCCACCGGAACTCNCAANGTGCGCTCATCGGGCTCTACGCGCCATCTTCCCCGGATTCTTCGCGGCNGNGTNCCGNGGGACCCCGGACTGTGACNGGCCCAACGGCCAACACCGCACTGTGACNGGCCCAACGGCCAACACACACGCCAACACACACGCAACTCTCCCGGATTCTTCCCCGGATTCTTCGCGCCNGNGTNCCGNGGGACCCCGGACTGTGACNGGCCCAACGGCTCATCATCG

CCGGATAGCGGTGTCTGAACTTCGCCCGTTCCCTCCANCGCATTGAGCTTCAGCCCGACCGGCAGGTNNGGAGTCGGC
ATGCGGTCCTTCGCCCCGACCCCGCTGGCTAAATANCCACCCCCGAGCGCGGTCACGGTCTTTGCACCGGGACGACGC
ATACCGGCAGCGCGAACATCNCCGCGGGCTGCAGCNTGAACGTCCAATACCANTCNAACAGTGTCCGCGCGTNAAAAC
CCGANCCGGCGGTCGCTTCNGTAATCAACGGCTCCTGCGCAACCAGCTGCAAGTCGCCGGTGCCACCGGCGTTGACGA
TCTTGATGTCTGCGANCTCGCGCACCAGCTCGACGGCCCGGGCA

Clone Rv96

Clone Rv9



Table 4: End-sequences of the polynucleotide inserts cloned in the named recombinant BAC vectors contained in the I-2049 M. bovis strain Pasteur genomic DNA library.

RvXXXSP6 corresponds to the SP6 end-sequence of the clone RvXXX.

RvXXXT7 corresponds to the T7 end-sequence of the clone RvXXX.

RvXXXIS 1081 corresponds to a region located close to a copy of the IS1081 repetitive sequence (Insertion element).

The character « - » denotes an uncertain base residue.

AAG-

TCGGGTTTCCACACGCGCGGTTTGACCCTAGTCATATGTAATCATGTGTACCATGTGCGGGCGCTTTTCGACGGCCGCGCGCACCCGGA-ATTTCCTGTGATTTCACTGCATGCGTACCATCTGGCACAATTGAGCA-TTGTCT-

TCGCGGTGGTCGG-CGGGTTGCGTGCCGCCTGCTGCGA-ATGCACCA-

TAAGCCCGAACCCACCGGCTTGGTGACCACCGCACGCTGCGTGTGGGGGGGTAACCACTCCGCGACCCCAAGGATGGTCATTTCCAATGAACCGGCTGGACTTCGTCCA-A

## Clone X0002

GTGCAGGTTTCGACAATGTGGTGCCGGTTCGGCGGCTACGTGCCATCGAGACACTGGCGCA-GCTATCGCACCCGTT
ATCGGCTGCGAGCAAATCGCGGTATGCGTTCTTGAGCATGAGTCGGCGACCGTCGTCATGGTCGACACCCACGACGG
AAAGACGCAGATCGCCGTCAAGCATGTGTGCCGCGGATTATCAGGACTGACCTCCTGGCTGACCGGCATGTTTGGTC
GCGATGCCTGGCGCCCGGCCGGCGTGGTCGTCGGCTCGGATAGCGAGGTCAGCGAATTCTCGTGGCAGCTCGAA
AGGGTCCTGCCGGTGCCGGT

Clone X0003

TTCGAGTCATGCGCCCGCCTCGACCACGAA-ATGCACGTCG-

GGTTCGATCGACCCGATCTTCACCTCGTAACCTCGATGCTTAGCAGGATCCAGCTTGACCGCGTTTGGCTCTACCCACTTTGAGTGGCGCCGTCGCCTGTGCCCCATCGGTGTTCATGACGAACGCTTCGAAAGAACTTCCTCTTGTGAGCCGCAATGTCTGCGTAAAGAAGTTCCATGTCCGGGAAGTAGACCCGGTCGCCCTCCACGTGGTACTCCTTCGAGGTCCGCCTTCTC

Clone X0004

AACAGCGCGGTTGAACTGATAGGTĞCGGCCCGGCTCGAGCAGGCCGGCCATTTGTTCGATGCGGTTACCGAAAGAT CTCTTCGGTGACCTGCCCGCCGCCGGCCAGCTCGGCCCAGTGCCCGGCGTTGGCCGCGGCGACGATCTTGGCGT CCACGGTGGTCGGGG

Clone X0006

Clone X0007

ATCGGTTTCCAGCAACAGCCGATCGACGGCTTCGCCCA-

GGCCGCTCCCGGGCGACCCATTGCTGTCGCCGCGTAACGCCATCACGGATGACGCGCAGTTCGTCGTCTAGCCCACCATCGCCTGCACACCGGCGGCCAG-ACCCATTGGCCGTCGCACTCGTA-

AGCAGGTAATCCTCGTCGACGGACTCGGTAACCACCGCCGCCAGCTCCGCTGCCAGGTCGGCGGGGTTGACACCGGCGGCATCGGGATGGACGACGACGACGCGTGCTGACGGCGCTGTC

AGCGGTTTCCCA-

Clone X0008

::::::::::X0008SP6.seq:::::::::::

TGGACCTCATGACAACGCGGCGGCGATTACCCCCGCTACCGCCAGCAGCAGCAGCAGCGCGGTAGCGAACACCGCCGGAT GCAGCGCAGGTGCGTCGATGTGCTCACGGAATCGCCCCGGCACCGCGATCTCGAGGATCACCAGTGCCACCCCCTGC AGCGCGACCCCGACGACGCCGACGCCGATCAGGCCCAGCTGGCCAGCTGGCGATAATGGCGGCGATGGTG ACGATGGCCAGCCCACATACATTGTGGCGGCCAGAACCACGGCGTTGGGGCGGGTCGATGAACACTAGGCGACG CAGATCGCCCGGGGTCAACAGGTTGACCATCAGAAAGCCTGCGA

Clone X0009

TTTGGTGCGGCCGGCAATCAACTTC-GCTC-

CAGCGGTTTCCCAGGCGGGATGTGCTGTGAGCGCCGCACCACCAGCGCCGACGCTAAGGATGGAACGCACGGCATCT
TCTGACGCGTAACCGCGTTGTGATCGCGAGCTGAGGAGACGGTATGGGGAGGGTTCTCGGAGGCCATCTGGGATGT
TGATGTCTGTCGATCTTGAGCCGGTGCAACTCGTCGGCCCGGACGGTACGCCGACGGCCGAACGCCGCTACCACCGT
GACCTTCCTGAGGAAACGCTGCGTTGGCTCTACGATATGATGGTGGTCACCCG

#### Clone X0010

AATACTCAATCTTGATCGGTTTCCAGCAACAGCCGATCGACGGCTTCGCCCAGGGCCGCTCCCGGGCGACCCACCA TTGCTGTCGCCGCGTAACGCCATCACGGATGACGCGCAGTTCGTCGTCGTCTCACCATCGCCTGCACACCGG CGGCCAGGACCCATTGGCCGTCGCACTCGTAGAGCAGGTAATCCTCGTCGACGGACTCGGTAACCACCGCCGCCAGC TCCGCTGCCAGGTCGGCGGGGTTGACACCGGCGGGCATCGGGATGGACGACGCGGTGCTGACGGCGCCTGTCGC GACTCTGAGCTCGG

# Clone X0012

 $\label{eq:condition} \begin{tabular}{ll} ATCACGACAGCGGCGGCGCCCCGTTGCCGGGCAATGTTGAGGCGTTTCTGCGTCTGGTTGAGGCCGGCTGGGAC-\\ \end{tabular}$ 

GCGGCTACGTGCCATCGAGACACTGGCGCAGGCTATCGCACCCGTTATCGGCTGCGAGCAAATCGCGGTATGCGTTC
TTGAGCATGAGTCGGCGACCGTCATGGTCGACACCCACGACGGAAAGACGCAGATCGCCGTCAAGCATGTGTGC
CGCGGATTATCAGGACTGACCTCCTGGCTGACCGGCATGTTTTGGTCGCGATGCCTG:

#### Clone X00013

# Clone X0014

 $\label{eq:condition} \textbf{AGCGGCTGGTTACGACTCCCTGTTTGTGATGGACCACTTCTACCAACTGCCCATGTTGGGGACGCCCG-CC-TCGATGCTGGAAGCCTACACTGCCCTTGGTGCCC-C-GCGACCGAGCGGCTGCAACTGGGCGC-TTGGTGACC-GCAATACCTACCGCACCCC-ACCCTGCTGG-CAAA-$ 

ATCATCACCACGCTCGACTTGGTTAGCGCCGGTCGA-CGATCCTCGGCATTGGAACCGGTTGGTTT-

### Clone X0015

Clone X0016

CAGGCGTGCAATGACCTGCACTGCGCCGGA-A-

TCCCTAACCCACTAAACCGGGGCCGCTCACAAGCCGTGCAGCTCAGCGTCAGGTGCGCGACCAGGAATAAATGAGCAGACCCGTGCCGTCAACGATGGTGGCGATCATCGGCCCCGAAACGATGGCCGGGTCATGCGCAACTTCTTCAGCAGCGGCGGAAGGACGGCA-CCACCAGCGAC-ACCACCACCACGAT

Clone X0017

TTGGGC-TTGCCC-CAATA-GGCCCCAATCAAAAGCCGAGCAGGTGGAACCTA-CGCATTCGCCTC-TCGT-

TGTGCACCCGAGCCATCGCACGCGCGGGAATTCCCGGAT-TC-

CCGTATTCTCCGGCGGCCGGGCTAACCCATCCCA-GCCGAACGGTTGGCTC-

 ${\tt TGCCGTGGGTCCCGTGTTGGCCGATCGGGGGCGTCACCGGGGGGTGCTCGGGTGCGG-TGACCATGGC-AACTGCCCC-ATGGGCCGACCCTGGTGCAGATAAACCTG}\\$ 

TGGTGGAGGTCCCCACCAA-ACCCGGCCGTAACTCTGCTCACGGAAATGCGG-

CAGGCCGCGCGTAGCACGTGGTATCCGCCATAAAGGTGCACCTTAAGCACGGCGTCCCAATTCTCGAACGACATCTT
GTGGAAGGTGCCGTCGCGCAAGATCCCGGCGTTGCTCACCACACCGTGCACGGCGCGAATTCGTCAAGCGCGGTCT
TGATGATGTTCGCTGCGCCGTCCTCGGTGGCGACGCTGTCGGTA-

TTGGCGACCGCCCGGCCCCTTGTCGCGAAATCTCGGCGACGACCTCATCGGCCATCGCCGAACCGGGCGCCCG

Clone X0018

GCCGGCCAAACTGGCCGGCGGGGTTGCTGTC-TCAAGGTGGGTTCCGCCACCAA-ACC-

CACTCAAGGATCGCAAGGAAAGC-

TCAAGGATGCGGTCGCGGCCCAAGGCCGCGGTCAAGGAGGCCATCGTCCCTGGTGGGGGACCTCCCTCATCCACCAGGCCCGCAAGGCGCTGACCGAACTGC-TGCGTC-C-GACCGGTGACAAGTCCTCGGTGTCCACGTGT-CTCCGAAGCCCTTGCCGCTCCGTTGTTCTGGATC-CC-CCAACCTGGCTTGGACGGCTC-GTGGTGGTCAACAAGGTCAGCGAGCTACCCGCCGGGCATGGGCTGAACGTGA

Clone X0018

CGAACCT-AATTGTCCTGTAATGCCCAGCTCACCAA-

GCATGGCTGGTGGCCGGGCGTGAAGCCGGCGTCTGCGGCACCGTCCAACTC-ATGTGGAT-

GCCGGAATGGGGATGTCCGG-ACGGCGAATCCGTA-

TTCGCTTGTCCCGTGAGGCCCAGGTGGATGGGGGGAAGGATC-TGGTGTCCGGGATGAT-

ATGGGGCCGATGCCGCCGGTTGAAGTCCACTGGATCGGGAATTCGGGAATCGTGAT-CCGACGTTCAGGCCGAAC

Clone X0019

CTAACGGAATGAAAGCCCTGGTGGCCGT-

 ${\tt TCGGCGTGGCCGTCGCACTGCTCGGTGTATCTTCCGCCCAAGCTGATCCCGAGGCGGATCCCGGCGCAGGTGAGGCCAACTATGGTGGCCCCCCAAGTTCCCCACGTCTTGTCGATCACACCGAATGGGCGCA-}$ 

TGGGGAATTCTGCCCAGCCTCCGGGTCTACCCGTCCCAAGTTGGGCGTACA-

CCTCCCGCCGCCTCGGGATGGCCGCTGCCGACCCGGCCTGGGCC-

AGGTTCTCGCGCTGTCACCGGAAGCCGACACTGCCGGC

CCGCGGGACAC-CCTC-

Clone X0020

CTCTGGGACCGGCCACGGTGCC-

CCGGCGTTCCCGGACGTGCTGCGCCAGGTGTCCGGCGGCCGCTGCATGGTGTTCCCGGATCGGCCGCTGGCCAGAGCCCACCGGTGAATCTGGCGCCTGGCCACCACCGTGCGCCTAGGCTTGCGATCGTGCAGCGCTGGCCAGGACCACCGTGCGCCTAGGCTTGCGATCGTGCACCGCGGGCACGCCGAACCGAGATCCCGACGGATTGGGGCAGATGCGTGCTCACCATCGGGGTATTTGACGGCGTGCACCGCGGGCACGCCGAACTGATCGCGCACGCGGTCAAAGGCGGC

Clone X0021

 ${\tt TCGACCTCGAGTGAATGGATCTCGAGTGAATGGACAGGGCATCGCCTACGAGTCGCATCCCATCCAACAGACCGGTGCTTTGCATCGGACCCTGAAGGTCCCGCACGGAGGGTGTGCTTGCCGGCGCGGGGTCACGGTGCGGTAGCGACGTAGTTTTGAACGAATTTCTTGATGCTCCAACCTGTTTGGTGTTCAATCCAGTTCT$ 

Clone X0175

....X0175SP6.....

AA-CTTGCGCGCTCGGCCGGGTC-AGCATCCAGCTGCTCGGCAAGGAGGCCAGCTAC-C-

TCGCTGCGTATGCCCAGCGGTGAGATCCGCCGGGTC-

ACCACCGCACGGCGTGGTGAGGGTAAAACCTCCGGCGGCCGTCACCCGGTTAGCCCGTGGGGCAA

....X0175T7....

# References:

Altschul, S. F., W. Gish, W. Miller, E. W. Myers, and D. J. Lipman. 1990. Basic local alignment search tool. J. Mol. Biol. 215:403-10.

Balasubramanian, V., M. S. Pavelka, Jr., S. S. Bardarov, J. Martin, T. R. Weisbrod, R. A. McAdam, B. R. Bloom, and W. R. Jacobs, Jr. 1996. Allelic exchange in Mycobacterium tuberculosis with long linear recombination substrates. J. Bacteriol.

178:273-279.

Barany F., 1991, Proc. Natl. Acad. Sci. USA, 88:189-193.

Bensimon, A., A. Simon, A. Chiffaudel, V. Croquette, F. Heslot, and D. Bensimon.

10 1994. Alignment and sensitive detection of DNA by a moving interface. Science 265.2096-2098.

Bergh, S., and S. T. Cole. 1994. MycDB: an integrated mycobacterial database. Mol. Microbiol. 12:517-534.

Birnboim, H. C. and J. Doly. 1979. A rapid alkaline extraction procedure for screening recombinant plasmid DNA. Nucleic Acids Res. 7:1513-1523.

Burg J.L et al., 1996, Mol. and Cell. Probes, 10:257-271.

Cai, L., J. F. Taylor, R. A. Wing, D. S. Gallagher, S. S. Woo, and S. K. Davis. 1995. Construction and characterization of a bovine bacterial artificial chromosome library. Genomics. 29:413-425.

Canard, B., and S. T. Cole. 1989. Genome organization of the anaerobic pathogen Clostridium perfringens. Proc. Natl. Acad. Sci. USA 86:6676-6680.

Chu B.C.F. et al., 1986, Nucleic Acids Res., 14:5591-5603.

Chuang S. et al., 1993. Global regulation of gene expression in *Escherichia coli*. J. Bact., 175(7): 2026-2036.

- 25 Chuang, S., D. L. Daniels, and F. R. Blattner. 1993. Global regulation of gene expression in Escherichia coli. J. Bacteriol. 175:2026-2036.
  - Cole, S.T., R. Brosch, K. Eiglmeier, T. Garnier, S. V. Gordon, C. Churcher, D. Harris, K. Badcock, D. Basham, D. Brown, T. Chillingworth, R. Connor, R. Davies, K. Devlin, T. Feltwell, S. Holroyd, S. Gentles, K. Jagels, J. McLean, S. Moule, L. Murphy, K.
- Oliver, J. Osborne, J. Parkhill, M. Quail, M-A. Rajandream, J. Rogers, S. Rutter, K. Seeger, J. Skelton, R. Squares, S. Squares, J. Sulston, K. Taylor, S. Whitehead and B.

G. Barrell. 1997. Genome Sequence of Mycobacterium tuberculosis H37Rv. Microbial Comparative Genomics, 2:174.

129

Collins, D. M., and D. M. Stephens. 1991. Identification of an insertion sequence, IS1081, in Mycobacterium bovis. FEMS Microbiol. Lett. 67:11-15.

- 5 Cousins D. et al., 1998, **36**(1): 168-170.
  - De Wit D. et al., 1990, J. Clin. Microbiol., 28: 2437-2441.
  - Dear, S., and R. A. Staden. 1991. Sequence assembly and editing program for the efficient management of large projects. Nucleic Acids Res. 19:3907-3911.
  - Duck P. et al., 1990, Biotechniques, 9:142-147.
- 10 Guateli J.C. et al., 1990, Proc. Natl. Acad. Sci. USA, 87:1874-1878.
  - Kievitis T. et al., 1991, J. Virol. Methods, 35:273-286.
  - Kim, U. J., B. W. Birren, T. Slepak, V. Mancino, C. Boysen, H. L. Kang, M. I. Simon, and H. Shizuya. 1996. Construction and characterization of a human bacterial artificial chromosome library. Genomics. 34:213-218.
- Kwoh D.Y. et al., 1989, Proc. Natl. Acad. Sci. USA, 86:1173-1177.
   Landegren U. et al., 1988, Science, 241:1077-1080.
   Liu, Y. G., and R. F. Whittier. 1995. Thermal asymmetric interlaced PCR: automatable
  - amplification and sequencing of insert end fragments from P1 and YAC clones for chromosome walking. Genomics. 25:674-681.
- 20 Lizardi P.M. et al., 1988, Bio/technology, 6:1197-1202.
  - Matthews J.A. et al., 1988, Anal. Biochem., 169:1-25.
  - Michalet, X., R. Ekong, F. Fougerousse, S. Rousseaux, C. Schurra, N. Hornigold, M. Vanslegtenhorst, J. Wolfe, S. Povey, J. S. Beckmann, and A. Bensimon. 1997. Dynamic molecular combing stretching the whole human genome for high-resolution studies.
- 25 Science. 277:1518-1523.
  - Misumi, D. J., D. L. Nagle, S. H. McGrail, B. J. Dussault, Jr., J. S. Smutko, H. Chen, O. Charlat, G. M. Duyk, C. Ebeling, L. Baldini, G. A. Carlson, and K. J. Moore. 1997. The physical and genetic map surrounding the Lyst gene on mouse chromosome. Genomics. 40:147-150.

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Pavelka, M. S., Jr., and W. R. Jacobs, Jr. 1996. Biosynthesis of diaminopimelate, the precursor of lysine and a component of peptidoglycan, is an essential function of Mycobacterium smegmatis. J. Bacteriol. 178:6496-6507.

Philipp, W. J., S. Nair, G. Guglielmi, M. Lagranderie, B. Gicquel, and S. T. Cole. 1996a.

Physical mapping of Mycobacterium bovis BCG pasteur reveals differences from the genome map of Mycobacterium tuberculosis H37Rv and from M. bovis. Microbiology. 142:3135-3145.

Philipp, W. J., S. Poulet, K. Eiglmeier, L. Pascopella, V. Balasubramanian, B. Heym, S. Bergh, B. R. Bloom, W. R. Jacobs, Jr., and S. T. Cole. 1996b. An integrated map of the genome of the tubercle bacillus, Mycobacterium tuberculosis H37Rv, and comparison with Mycobacterium leprae. Proc. Natl. Acad. Sci. USA. 93:3132-3137.

Poulet S. et al., 1995, Arch. Microbiol., 163: 87-95.

Ross BC, 1992, J. Clin. Microbiol., 30: 942-946.

Sambrook, J., E. F. Fritsch, and T. Maniatis. 1989. Molecular cloning: a laboratory manual, 2nd ed. Cold Spring Harbor Laboratory, NY: Cold Spring Harbor. N. Y.

Sanchez-Pescador R., 1988, J. Clin. Microbiol., 26(10):1934-1938.

Segev D., 1992, in « Non-radioactive Labeling and Detection of Biomolecules ». Kessler C. Springer Verlag, Berlin, New-York, 197-205.

Sheng, Y., V. Mancino, and B. Birren. 1995. Transformation of Escherichia coli with large DNA molecules by electroporation. Nucleic Acids Res. 23:1990-1996.

Shinnick T.M. et al., 1987, J. Bact., 169(3): 108-1088.

Shizuya, H., B. Birren, U. J. Kim, V. Mancino, T. Slepak, Y. Tachiiri, and M. Simon. 1992. Cloning and stable maintenance of 300-kilobase-pair fragments of human DNA in Escherichia coli using an F-factor-based vector. Proc. Natl. Acad. Sci. USA. 89:8794-

25 8797.

Spargo C.A. et al., 1996, Mol. and Cell. Probes, 10:247-256.

Stone B.B. et al., 1996, Mol. and Cell. Probes, 10:359-370.

Trieselman B.A. et al., 1992. Transcriptionnally active regions in the genome of the archaebacterium *Haloferax volcanii*. J. Bact., **174**: 30-34.

Trieselmann, B. A., and R. L. Charlebois. 1992. Transcriptionally active regions in the genome of the archaebacterium Haloferax volcanii. J. Bacteriol. 174:30-34.

Urdea M.S. et al., 1991, Nucleic Acids Symp. Ser., 24:197-200.

Urdea M.S., 1988, Nucleic Acids Research, 11: 4937-4957.

Van Soolingen D., 1993, J. Clin. Microbiol., 31: 1987-1995.

Willets, N., and R. Skurray. 1987. Structure and function of the F-factor and mechanism
 of conjugation. In Escherichia coli and Salmonella Typhimurium: Cellular and Molecular Biology (F.C. Neidhardt, Ed) Vol.2 pp1110-1133, Am. Soc. Microbiol., Washington, DC.

Woo, S. S., J. Jiang, B. S. Gill, A. H. Paterson, and R. A. Wing. 1994. Construction and characterization of a bacterial artificial chromosome library of Sorghum bicolor. Nucleic Acids Res 22:4922-4931.

Zimmer, R., and A. M. V. Gibbins. 1997. Construction and characterization of a large-fragment chicken bacterial artificial chromosome library. Genomics. 42:217-226.

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# **CLAIMS**

- 1. A method for isolating a polynucleotide of interest that is present in the genome of a mycobacterium strain and/or is expressed by said mycobacterium strain and that is absent or altered in the genome of a different mycobacterium strain and/or is not expressed in said different mycobacterium strain, said method comprising the use of at least one clone belonging to a genomic DNA library of a given mycobaterium strain, said DNA library being cloned in a bacterial artificial chromosome (BAC) vector.
- 2. The method according to claim 1, wherein the BAC-based DNA library has been constructed from genomic DNA of *Mycobacterium tuberculosis*.
- 3. The method according to claim 2, wherein the BAC-based DNA library has been constructed from genomic DNA of *Mycobacterium tuberculosis* strain H37Rv.
- 4. The method according to claim 3, wherein the BAC-based DNA library has been deposited in the Collection Nationale de Cultures de Microorganismes (CNCM) on November 19, 1997 under the accession number I-1945.
- 5. The method according to claim 1, wherein the BAC-based DNA library has been constructed from genomic DNA of *Mycobacterium bovis*.
- 6. The method according to claim 5, wherein the BAC-based DNA library has been constructed from the genomic DNA of *Mycobacterium bovis* BCG strain Pasteur.
- 7. The method according to claim 6, wherein said DNA library contains approximatively 1600 clones and wherein the genomic DNA is cloned into a recombinant pBeloBAC11 vector with an average insert size of approximately 80 kb.
- 8. The method according to claim 6 or 7, wherein the at least one BAC-based DNA library has been deposited in the Collection Nationale de Cultures de Microorganismes (CNCM) on June 30, 1998 under the accession number I-2049.

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9. A method of isolating a polynucleotide of interest that is present in a genome of a first mycobacterium strain or that is expressed by the first

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mycobacterium strain and that is absent or altered in a genome of a second

mycobacterium strain or that is not expressed by the second mycobacterium

- 5 strain, said method comprising:
  - a) providing at least one polynucleotide contained in a clone of a bacterial artificial chromosome (BAC) DNA library of the first mycobacterium strain;
  - b) providing at least one genomic or cDNA polynucleotide from a second mycobacterium strain that is different from the first mycobacterium strain or at least one polynucleotide contained in a clone of a BAC DNA library prepared from the genome of the second mycobacterium strain;
  - c) contacting under hybridizing conditions the polynucleotide of step a) with the polynucleotide of step b); and
  - d) isolating the polynucleotide of step a) that has not formed a hybrid complex with the polynucleotide of step b).
  - 10. The method of claim 9, wherein the polynucleotide contained in a clone of a BAC DNA library of the first or second mycobacterium strain is prepared by the following procedure:
  - 1) digesting at least one recombinant BAC clone by an appropriate restriction endonuclease to yield a polynucleotide insert of interest; and
    - 2) isolating the polynucleotide insert of interest.
    - 11. A purified polynucleotide of interest that has been isolated according to the method of claim 9.
- 12. The purified polynucleotide of claim 11 which contains at least one
  25 Open Reading Frame (ORF).
  - 13. The purified polynucleotide of claim 12, which is SEQ ID N0:1.
  - 14. The purified polynucleotide of claim 12, wherein said polynucleotide is selected from the group consisting of:

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- a) a polynucleotide comprising at least 8 consecutive nucleotides of SEQ ID N0:1;
- b) a polynucleotide having a sequence fully complementary to SEQ ID N0:1; and
- c) a polynucleotide that hybridizes under stringent hybridization conditions with the polynucleotide defined in a) or with the polynucleotide defined in b).
  - 15. The purified polynucleotide of claim 14, which is SEQ ID N0:2.
  - 16. The purified polynucleotide of claim 14, which is SEQ ID N0:3.
- 17. The purified polynucleotide of claim 12, wherein the ORF encodes all or part of a polypeptide involved in the pathogenicity of a mycobacterium strain.
- 18. The purified polynucleotide of claim 12, wherein the ORF encodes all or part of a Polymorphism Glycine Rich Sequence (PGRS).
  - 19. The purified polynucleotide of claim 18, which is SEQ ID N0:4.
- 20. The purified polynucleotide of claim 18, which is selected from the group consisting of:
- a) a polynucleotide comprising at least 8 consecutive nucleotides the of SEQ ID N0:5;
  - b) a polynucleotide having a sequence that is fully complementary to SEQ ID N0:5;
  - c) a polynucleotide that hybridizes under stringent hybridization conditions with the polynucleotide defined in a) or with the polynucleotide defined in b).
    - 21. A pair of the purified polynucleotides as claimed in claim 11.
    - 22. A Mycobacterium tuberculosis strain Rv37 genomic DNA library that has been deposited in the Collection Nationale de Cultures de Microorganismes under accession number I-1945, wherein said genomic DNA library comprises recombinant bacterial artificial chromosome vectors.
    - 23. A recombinant bacterial artificial chromosome (BAC) vector, which belongs to the genomic DNA library of claim 22.
    - 24. The recombinant BAC vector of claim 23, which is selected from the group consisting of:

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Rv101; Rv102; Rv103; Rv104; Rv105; Rv106; Rv107; Rv108; Rv109; Rv10; Rv110; Rv111; Rv112; Rv113; Rv114; Rv115; Rv116; Rv117; Rv118; Rv119; Rv11; Rv120; Rv121; Rv122; Rv123; Rv124; Rv126; Rv127; Rv128; Rv129; Rv130; Rv132; Rv134; Rv135; Rv136; Rv137; Rv138; Rv139; Rv13; Rv140; Rv141; Rv142; Rv143; Rv144; Rv145; Rv146; Rv147; Rv148; Rv149; Rv14; Rv150; Rv151; Rv152; Rv153; Rv154; Rv155; Rv156; Rv157; Rv159; Rv15; Rv160; Rv161; Rv162; Rv163; Rv164; Rv165; Rv166; Rv167; Rv169; Rv16; Rv170; Rv171; Rv172; Rv173; Rv174; Rv175; Rv176; Rv177; Rv178; Rv179; Rv17; Rv180; Rv181; Rv182; Rv183; Rv184; Rv185; Rv186; Rv187; Rv188; Rv18; Rv190; Rv191; Rv192; Rv193; Rv194; Rv195; Rv196; Rv19; Rv1; Rv201; Rv204; Rv205; Rv207; Rv209; Rv20; Rv214; Rv215; Rv217; Rv218; Rv219; Rv21; Rv220; Rv221; Rv222; Rv223; Rv224; Rv225; Rv226; Rv227; Rv228; Rv229; Rv230; Rv231; Rv232; Rv233; Rv234; Rv235; Rv237; Rv240; Rv241; Rv243; Rv244; Rv245; Rv246; Rv247; Rv249; Rv24; Rv251; Rv252; Rv253; Rv254; Rv255; Rv257; Rv258; Rv259; Rv25; Rv260; Rv261; Rv262; Rv263; Rv264; Rv265; Rv266; Rv267; Rv268; Rv269; Rv26; Rv270; Rv271; Rv272; Rv273; Rv274; Rv275; Rv276; Rv277; Rv278; Rv279; Rv277; Rv280; Rv281; Rv282; Rv283; Rv284; Rv285; Rv286; Rv287; Rv288; Rv289; Rv28; Rv290; Rv291; Rv292; Rv293; Rv294; Rv295; Rv296; Rv29; Rv29; Rv301; Rv302; Rv303; Rv304; Rv306; Rv307; Rv308; Rv309; Rv30; Rv310; Rv311; Rv312; Rv313; Rv314; Rv315; Rv316; Rv317; Rv318; Rv319; Rv31; Rv32; Rv322; Rv327; Rv328; Rv329; Rv32; Rv330; Rv331; Rv333; Rv334; Rv335; Rv336; Rv337; Rv338; Rv339; Rv33; Rv340; Rv341; Rv343; Rv344; Rv346; Rv347; Rv348; Rv349; Rv34; Rv350; Rv351; Rv352; Rv353; Rv354; Rv355; Rv356; Rv357; Rv358; Rv359; Rv35; Rv360; Rv361; Rv363; Rv364; Rv365; Rv366; Rv367; Rv368; Rv369; Rv36; Rv370; Rv371; Rv373; Rv374; Rv375; Rv376; Rv377; Rv378; Rv379; Rv37; Rv381; Rv382; Rv383; Rv384; Rv385; Rv386; Rv387; Rv388; Rv389; Rv389; Rv390; Rv391; Rv392; Rv393; Rv396; Rv39; Rv3; Rv40; Rv412; Rv413; Rv414; Rv415; Rv416; Rv417; Rv418; Rv419;

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Rv41; Rv42; Rv43; Rv44; Rv45; Rv46; Rv47; Rv48; Rv49; Rv4; Rv50; Rv51;

Rv52; Rv53; Rv54; Rv55; Rv56; Rv57; Rv58; Rv59; Rv5; Rv60; Rv61; Rv62;

Rv63; Rv64; Rv65; Rv66; Rv67; Rv68; Rv69; Rv6; Rv70; Rv71; Rv72; Rv73;

Rv74; Rv75; Rv76; Rv77; Rv78; Rv79; Rv7; Rv80; Rv81; Rv82; Rv83; Rv84;

5 Rv85; Rv86; Rv87; Rv88; Rv89; Rv8; Rv90; Rv91; Rv92; Rv94; Rv95; Rv96 and Rv9.

25. The recombinant BAC vector of claim 23, which is selected from the group consisting of:

Rv234; Rv351; Rv166; Rv35; Rv415; Rv404; Rv209; Rv272; Rv30; Rv228; Rv233; Rb38; Rv280; Rv177; Rv48; Rv374; Rv151; Rv238; Rv156; Rv92; Rv3; Rv403; Rv322; Rv243; Rv330; Rv285; Rv233; Rv219; Rv416; Rv67; Rv222; Rv149; Rv279; Rv87; Rv273; Rv266; Rv25; Rv136; Rv414; Rv13; Rv289; Rv60; Rv104; Rv5; Rv165; Rv215; Rv329; Rv240; Rv19; Rv74; Rv411; Rv167; Rv56; Rv80; Rv164; Rv59; Rv313; Rv265; Rv308; Rv220; Rv258; Rv339; Rv121; Rv419; Rv418; Rv45; Rv217; Rv134; Rv17; Rv103; Rv21; Rv22; Rv270; Rv267; Rv174; Rv257; Rv44; Rv71; Rv7; Rv27; Rv191; Rv230; Rv128; Rv407; Rv106; Rv39; Rv255; Rv74; Rv355; Rv268; Rv58; Rv173; Rv264; Rv417; Rv401; Rv144; Rv302; Rv81; Rv163; Rv281; Rv221; Rv420; Rv175; Rv86; Rv412; Rv73; Rv269; Rv214; Rv287; Rv42 and Rv143.

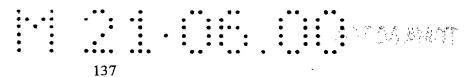
26. A *Mycobacterium bovis* BCG strain Pasteur genomic DNA library, wherein said genomic DNA library comprises recombinant bacterial artificial chromosome vectors.

27. A *Mycobacterium bovis* BCG strain Pasteur genomic DNA library according to claim 26, wherein said DNA library contains approximatively 1600 clones and wherein the genomic DNA is cloned into a recombinant pBeloBAC11 vector with an average insert size of approximately 80 kb.

28. A Mycobacterium bovis BCG strain Pasteur genomic DNA library according to claim 26, that has been deposited in the Collection Nationale de

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Cultures de Microorganismes (CNCM) on June 30, 1998 under the accession number I-2049.

- 29. A recombinant bacterial artificial chromosome (BAC) vector, which belongs to the genomic DNA library of claims 26 to 28.
- 5 30. A recombinant BAC vector according to claim 29, which is selected from the group consisting of:

X0001; X0002; X0003; X0004; X0006; X0007; X0008; X0009; X0010; X0012; X0013; X0014; X0015; X0016; X0017; X0018; X0019; X0020; X0021 and X0175.

- 31. A method for detecting a mycobacterial nucleic acid in a biological sample comprising the steps of:
  - a) contacting the recombinant BAC vector according to claim 23 or 29, or a purified polynucleotide according to claim 11 with the mycobacterial nucleic acid in the biological sample; and
  - b) detecting a hybrid nucleic acid molecule formed between said recombinant BAC vector or said purified polynucleotide and the mycobacterial nucleic acid in the biological sample.
  - 32. The method of claim 31, further comprising before step a), making the mycobacterial nucleic acid in the biological sample available to a hybridization reaction.
    - 33. A method for detecting mycobacterial nucleic acid in a biological sample comprising the steps of:
    - a) contacting a first polynucleotide according to claim 11 that has been immobilized onto a substrate with the mycobacterial nucleic acid in the biological sample; and
    - b) contacting a hybrid nucleic acid molecule formed between said first polynucleotide and the mycobacterial nucleic acid in the biological sample with a second, labeled polynucleotide according to claim 11, wherein said

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second polynucleotide and said first polynucleotide have non-overlapping sequences.

- 34. The method of claim 33, further comprising before step a), making the mycobacterial nucleic acid in the biological sample available to a hybridization reaction.
- 35. The method of claim 33 or 34, further comprising before step b), removing the mycobacterial nucleic acid that is not hybridized with the immobilized first polynucleotide.
- 36. A method for detecting mycobacterial nucleic acid in a biological sample comprising the steps of:
- a) contacting the mycobacterial nucleic acid in the biological sample with a pair of purified polynucleotides according to claim 21;
- b) amplifying said mycobacterial nucleic acid; and
- c) detecting the amplified mycobacterial nucleic acid.
- 37. The method of claim 36, further comprising before step a), making the mycobacterial nucleic acid in the biological sample available to a hybridization reaction.
  - 38. A kit for detecting a mycobacterium in a biological sample comprising:
- a) a recombinant BAC vector according to claim 23 or 29, or a purified polynucleotide according to claim 11; and
- b) reagents necessary to perform a nucleic acid hybridization reaction.
  - 39. A kit for detecting a mycobacterium in a biological sample comprising:
- a) a recombinant BAC vector according to claim 23 or 29, or a first polynucleotide according to claim 11 that is immobilized onto a substrate;
- b) reagents necessary to perform a nucleic acid hybridization reaction; and
  - c) a second polynucleotide according to claim 11, wherein said second polynucleotide is radioactively or non-radioactively labeled, and wherein said second polynucleotide and said first polynucleotide have non-overlapping sequences.

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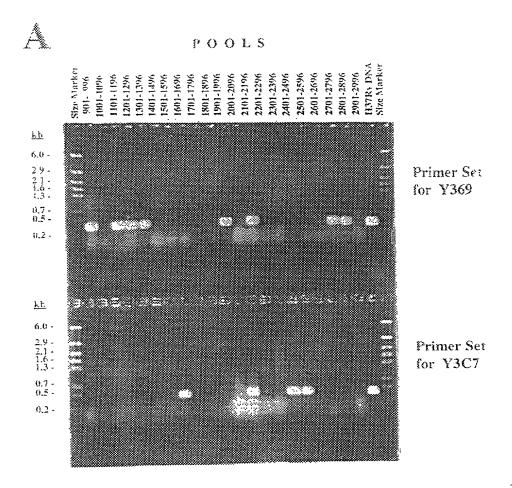


- 40. A kit for detecting a mycobacterium in a biological sample comprising:
- a) a pair of purified polynucleotides according to claim 20; and
- b) reagents necessary to perform a nucleic acid amplification reaction.
- 41. A method for detecting the presence of a genomic DNA, a cDNA or a mRNA of a mycobacterium in a biological sample, comprising the steps of:
  - a) contacting the biological sample with a plurality of BAC vectors according to claim 23 or 29, or purified polynucleotides according to claim 11 that are immobilized on a substrate; and
  - b) detecting the hybrid complexes formed.
- 42. A kit for detecting a genomic DNA, a cDNA or a mRNA of a mycobacterium in a biological sample, comprising:
- a) a substrate on which a plurality of BAC vectors according to claim 23 or 29, or purified polynucleotides according to claim 11 have been immobilized.
- 43. A method for detecting a polynucleotide of mycobacterial origin in a biological sample, said method comprising:
- a) aligning at least one polynucleotide contained in a recombinant BAC vector according to claim 23 or 29 on the surface of a substrate;
- b) contacting the polynucleotide in the biological sample with the substrate on which the polynucleotide of step a) has been aligned; and
- c) detecting a hybrid nucleic acid molecule formed between the polynucleotide in the biological sample and the aligned polynucleotide of step a).
  - 44. A kit for detecting a polynucleotide of mycobacterial origin in a biological sample, comprising:
  - a) a substrate on which at least one polynucleotide contained in a recombinant BAC vector according to claim 23 or 29 has been aligned.
  - 45. The method of claim 10, wherein the procedure by which the polynucleotide contained in a clone of a BAC DNA library is prepared, further comprises amplifying the polynucleotide insert.

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- 46. The method of claim 10, wherein the procedure by which the polynucleotide contained in a clone of a BAC DNA library is prepared, further comprises digesting the polynucleotide insert with at least one restriction endonuclease.
- 47. The method of claim 45, further comprising digesting the amplified polynucleotide insert with at least one restriction endonuclease.
- 48. The Polynucleotide of claim 17, wherein the mycobacterium strain is *Mycobacterium tuberculosis*.
- 49. The method of claim 36, wherein the amplified mycobacterial DNA is detected by gel electrophoresis or with a labeled polynucleotide according to claim 11.
  - 50. The kit of claim 40, further comprising a polynucleotide according to claim 11.
- 51. The kit of claim 42, further comprising reagents necessary to perform a hybridization reaction.
- 52. A method for physically mapping a polynucleotide of mycobacterial origin in a biological sample, said method comprising:
- a) aligning at least one polynucleotide contained in a recombinant BAC vector according to claim 23 or 29 on the surface of a substrate;
- b) contacting the polynucleotide in the biological sample with the substrate on which the polynucleotide of step a) has been aligned under hybridizing conditions; and
  - c) detecting the location of the hybridized polynucleotide from the biological sample.
- 53. The kit of claim 44, further comprising reagents necessary for labeling DNA and reagents necessary for performing a hybridization reaction.



# FIGURE 1A

B

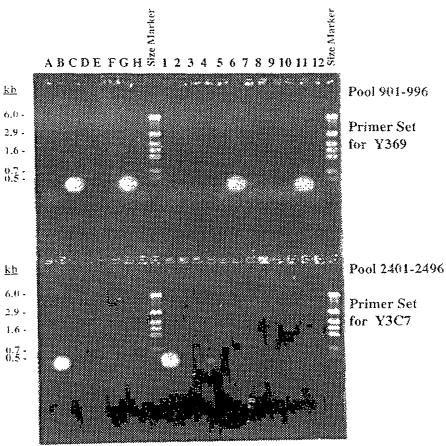


FIGURE 1B

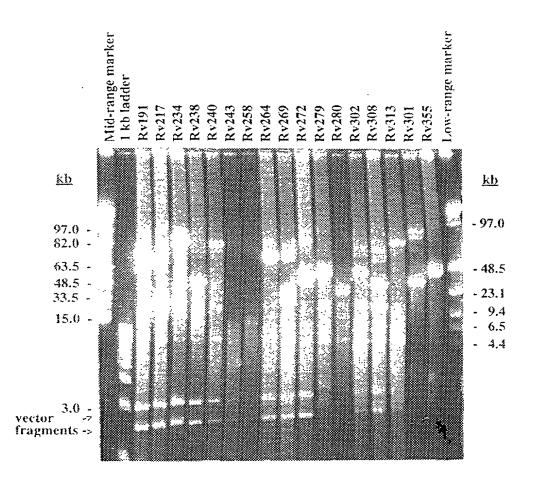


FIGURE 2

Mr. Ast.

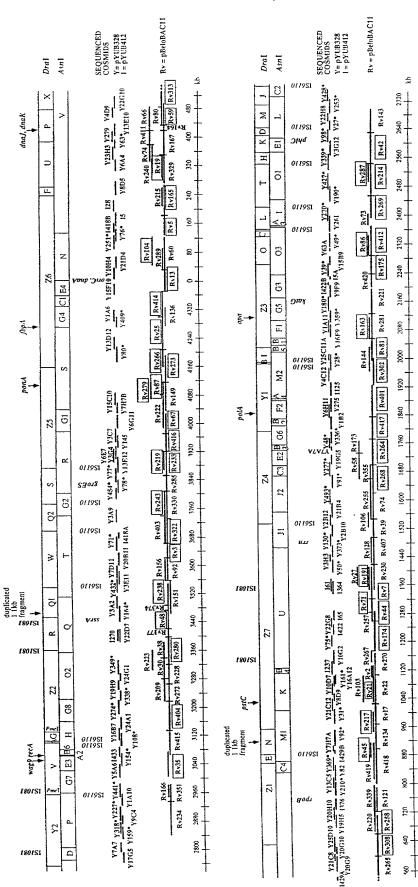
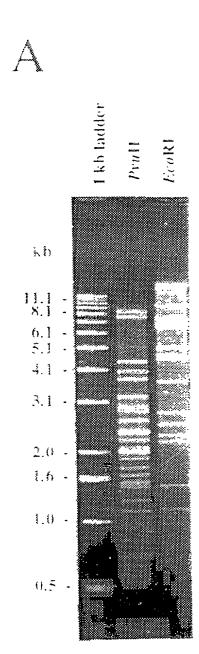


FIGURE 3

SUBSTITUTE SHEET (RULE 26)



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FIGURE 4A

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B

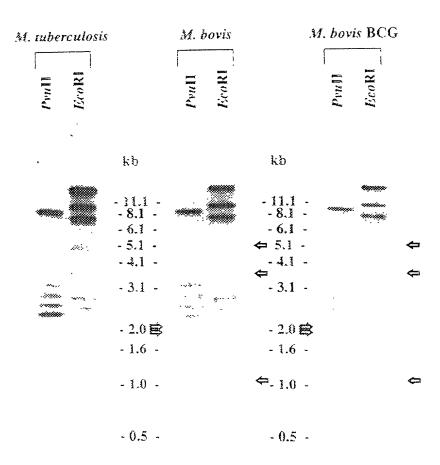


FIGURE 4B

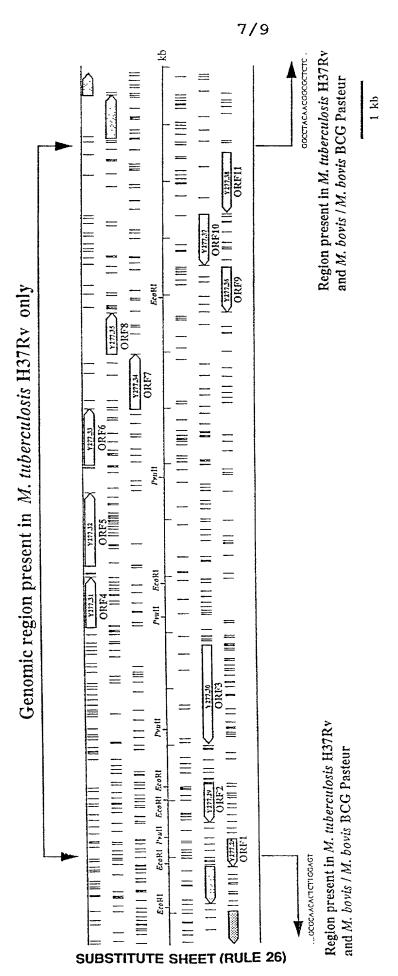


FIGURE 5

7 (7) 7 7 (7) 7 8 (4) 74

GYEGGAALSYGDTGGAGGYGGSAGLIGTGGAGGAGGTGANAGSPGTGGAGGLLLGQAGLAGLP 838047 PTQTLTGRPLIGNGTPGAYGSGATGAPGGNTLGDGGAGGSGAAGSGAPGGAGGAAGLNGT 837273 837813 GGAGGAGGSSAGGGAGGAGGALLGDGGAGGIGGASTYLGGTGGGGGYGGLYGAGGA GGAGGTGLYGGDGGAGGTGGLLAGLIGAGGGTGGTGGLSTNGDGGYGGAGGNAGHLA GGAGGTGLYGGDGGAGGTGGLLAGLIGAGGTGGTGGTGGLSTNGDGGYGGAGGNAGHLA H37RV GPGGAGGAGGDGENLDTGGDGGAGGSAGLLFGSGGAGGAGGFGFLGGDGGAGGNAGLLLS BCG GPGGAGGAGGDGENLDTGGDGGAGGSAGLLFGSGGAGGAGGFGFLGGDGGAGGNAGLLLS SGGAGGEGEETAGGYGGAGGHAGWLGEGAGGIGGIGGHAHGGAGGHGGTGGQLWGSGGA H37R4 BCG H37R9 H37RF H37R7 BCG BCG BCG BCG

## FIGURE 6

9/9

## pBeloBAC11

GEGGEGEAA GGGGTTCGCG TCAGCGGGTG TTGGCGGGTG TCGGGGCTGG Not I restriction site CTTAACTATG CGGCATCAGA GCAGATTGTA CTGAGAGTGC ACCATATGCG GTGTGAAATA CCGCACAGAT GCGTAAGGAG AAAATACCGC ATCAGGCGCC ATTCGCCATT CAGGCTGCGC AACTGTTGGG AAGGGCGATC GGTGCGGGCC TCTTCGCTAT TACGCCAGCT GGCGAAAGGGGGATGTGCTGCAAGGGGATT primer T7-BAC1 AAGTTGGGTA ACGCCAGGGT TTTCCCAGTC ACGACGTTGT AAAACGACGG CCAGTGAATEGTAATAGGACTCAGTATAGGGGGGAATTCGA GCTCGGTACC T7-promoter sequence CGGGGAICCT CTAGAGTCGA CCTGCAGGCA TGCAAGCTAG AGTATICTAT HindIII cloning site SP6-promoter AGTGTCACCT AAATAGCTTG GCGTAATCAT GGTCATAGCT GTTTCCTGTG sequence (complementary strand) primer SP6-Mid (complementary strand) TGAAATTGTT ATCCGCTCAC AATTCCACAC AACATACGAG CCGGAAGCAT AAAGTGTAAA GCCTGGGGTGGCTAATGAGT GAGCTAACTC ACATTAATTG primer SP6-BAC1 (complementary strand) CGTTGCGCTC ACTGCCCGCT TTCCAGTCGG GAAACCTGTC GTGCCAGCTG CATTAATGAA TCGGCCAACG CGAACCCCTT GCGGCCGC CC GGGCCGTCGA Not1 restriction site

## FIGURE 7

#3

nereby state that I have reviewed and understand the contents of the above-identified specification (in proceeding the claims, as amended by any amendment erred to above. I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56. hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) or any foreign application(s) for patent or inventor's certificate or § 365(a) any PCT international application(s) designating at least one country both than the United States, lated below and have sets is destrificate below, any foreign plication(s) for patent or inventor's certificate, or any PCT international application(s) designating at least one country both than the United States, lated below and have sets is destrificate below, any foreign plication(s) for patent or inventor's certificate, or any PCT international application(s) having a filing date before that of the application(s) of which priority claimed:  Country	s a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name; I believe I a riginal, first, and sole inventor (if only one name is listed below) or an original, first, and joint inventor (if plural names are listed below) of the subject of 1 signated and for which a patent is sought not the invention entitler. A method for 1 signating and for which a patent is sought not the invention entitler. A method for 1 signating and for which of the state of a mycobacterium using a BAC-based DNA 11brary. Application to the genome of a mycobacterium using a BAC-based DNA 11brary. Application to the specification of which of its attached and/or gwas filed on April 16, 1999  so understand the contents of the above-identified specification, including the claims, as amended by any amen element to above. I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56.  Thereby claim the profession price prements under 35 U.S.C. § 119(a) or § 356(b) of any foreign application(s) to patent or inventor's certificate or § 1 sany PCT international application(s) for patent or inventor's certificate, or any PCT international application(s) having a filting date before that of the application(s) of which is claimed:  Country Application Number Date of Filting Priority Claimed Under 35 U.S.C. § 119(a) of any United States application(s) in special papel and the papel cation(s) of which is claimed:  Country Application Number Date of Filting Priority Claimed Under 35 U.S.C. § 119(a) of any United States application(s) or § 365(c) of any PCT International application(s) of which is claimed:  Application Number Date of Filing Priority Claimed Under 35 U.S.C. § 119(a) of any United States application(s) or \$ 365(c) of any PCT International application(s) of the claims of this application is not disclosed in the prior United States, Instead below and, insofar as the subject matter of each of the claims of this application			Attorne	y Docket No	
inabl. first, and sole inventor (of only one name is listed below) or an original, first, and point inventor (if puris I annes are listed below) of the superior and its displant of for which a patient is sought on the invention entitled: A method, for the collection of the collecti	ignal, first, and sole inventor (if only one name is listed below) or an original, first, and joint inventor (if plural names are listed below) of the subject mich is claimed and for which a patent is sought on the invention entitled. A method for is all solating a polynucled of 1 mich is claimed and for which a patent is sought on the invention entitled. A method for is a considerable on the genome of a mycobacterium using a BAC-based DNA 11brary. Application to the genome of a mycobacterium using a BAC-based DNA 11brary. Application to the genome of a mycobacterium using a BAC-based DNA 11brary. Application to the genome of the genome o		DECLARATION AND P	OWER OF ATTORN	EY	
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hereby state that it have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any armediated to above. I acknowledge the duty to disclose information which in material to patentability as defined in 37 CFR 5.56. entirely again foreign priority benefits under 35 U.S.C. § 119(a)(d) or § 355(b) d any foreign application(s) or patent or inventor's certificate or § 305(s). Shereby gaten foreign priority benefits under 35 U.S.C. § 119(a)(d) or § 355(b) d any foreign application(s) for patent or inventor's certificate, or any PCT International application(s) having a filing date before that of the application(s) of which priority claimed.  Country Application Number Date of Filling Priority Claimed Under 35 U.S.C. 119  US 09/060 756 16/04/1998 Priority Claimed Under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:  Application Number Date of Filling Priority Claimed Under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:  Application Number Date of Filling Priority Claimed Under 35 U.S.C. § 119(e) of any United States application(s) or § 355(c) of any PCT International application(s) designating the lenses base, listed below and, morfar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application of the prior united States or PCT International application of the application of the prior united States or PCT International priority of the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application of the prior united States or PCT International application of the prior application of the prior united States or PCT International application of the prior priority of the prior priority of the policy of the prior priority of the priority of t	hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amenered to above. I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56. hereby claim foreign priority benefits under 35 U.S. C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate or § any PCT international application(s) designating at least one country other than the United States, listed below and have also identified below, any folication(s) for patent or inventor's certificate, or any PCT International application(s) having a filing date before that of the application(s) of which claimed:    Country		or PCT International Applicat	ion No. <u>PCT/1B99/00</u>		
BS 09/060 756 16/04/1998 PYES NO  hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:  Application Number Date of Filing  Application is not disclosed in the prior United States or PCT International application(s) designating the lited States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International polication(s) in the manner growthed by the first paragraph of 35 U.S.C. § 112. I acknowledge the duty to disclose information which is material paternability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application(s) and the national or PCT International right date of this application. Number Date of Filing Status (Patented, Pending, Abandoned)  Application Number Date of Filing Status (Patented, Pending, Abandoned)  Application Number Date of Filing Status (Patented, Pending, Abandoned)  Application Number Date of Filing Status (Patented, Pending, Abandoned)  Application Number Date of Filing Status (Patented, Pending, Abandoned)  Application Number Date of Filing Status (Patented, Pending, Abandoned)  Application Number Date of Filing Status (Patented, Pending, Abandoned)  Application Number Date of Filing Status (Patented, Pending, Abandoned)  Application Number Date of Filing Status (Patented, Pending, Abandoned)  Application Number Date of Filing Status (Patented, Pending, Abandoned)  Application Number Date of Filing Status (Patented, Pending, Abandoned)  Application Number Date of Filing Status (Patented, Pending, Abandoned)  Application Number Date of Filing Status (Patented, Pending, Abandoned)  Application Number Date of Filing Status (Patented, Pending, Abandoned)  Application Number Date of Filing Pending Number Date of Filing Number Date of Filing Number Date of Fili	US  O9/060 756  16/04/1998  PYES  NC  I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:  Application Number  Date of Filing  Application Number  Date of Filing  Application in the benefit under 35 U.S.C. § 120 of any United States application(s) or § 365(c) of any PCT International application(s) designat fined States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States (sternational application(s) in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is neglected in the prior application in 37 CFR § 1.56 which became available between the filing date of the prior application(s) and the national or PCT International application.  Application Number  Date of Filing  Status (Patented, Pending, Abandoned Pending), Abandoned Pending, Abandoned Pending, Abandoned Pending, Abandoned Pending, Abandoned Pending, Reg. No. 20,2021, Laurence R. Hetter, Reg. No. 25,327; Brian G. Brunsvold, Reg. No. 22,593; Tipton D. Jennings, IV, Reg. No. 26, 100, 100, 100, 100, 100, 100, 100, 10	hereby state that I have reviewed and underred to above. I acknowledge the duty hereby claim foreign priority benefits undany PCT international application(s) desolication(s) for patent or inventor's certification(s) for patent or inventor's certification(s)	inderstand the contents of the above to disclose information which is mader 35 U.S.C. § 119(a)-(d) or § 365 signating at least one country other	naterial to patentability as de b(b) of any foreign application than the United States, listed	efined in 37 CFR § 1 n(s) for patent or inve l below and have also	i.56. entor's certificate or § 365(a) o identified below, any foreign
hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:  Application Number  Date of Filing  Status (Patented, Pending, Abandoned)  Date of Filing  Date of Filing  Date of Filing  Status (Patented, Pending, Abandoned)  Date of Filing  Status (Patented, Pending, Abandoned)  Date of Filing  Date	Increby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:  Application Number  Date of Filing  Thereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) or § 365(c) of any PCT International application(s) designate interesting the states, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States stemational application(s) in the manner provided by the first paragraph of 35 U.S.C. § 112, l acknowledge the duty to disclose information which is not presentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application(s) and the national or PCT Interming date of this application.  Application Number  Date of Filing  Status (Patented, Pending, Abandoned  Poster of Filing  Poster of Filing  Status (Patented, Pending, Abandoned  Poster of Filing  Poster of Filing  Status (Patented, Pending, Abandoned  Poster of Filing  Poster of Filing  Status (Patented, Pending, Abandoned  Poster of Filing  Poster	Country	Application Number	Date of Filing	Priority Clai	imed Under 35 U.S.C. 119
Application Number  Date of Filing  Status (Patented, Pending, Abandoned)  Date of Filing  Date of Filing  Date of Filing  Status (Patented, Pending, Abandoned)  Date of Filing  Date of Filing  Date of Filing  Status (Patented, Pending, Abandoned)  Date of Filing  Date of Filing  Date of Filing  Status (Patented, Pending, Abandoned)  Date of Filing  Date of Filing  Date of Filing  Status (Patented, Pending, Abandoned)  Date of Filing  Date of Filing  Date of Filing  Status (Patented, Pending, Abandoned)  Date of Filing  Date of Filing  Date of Filing  Status (Patented, Pending, Abandoned)  Date of Filing  Date of Filing  Status (Patented, Pending, Abandoned)  Date of Filing  Status (Patented, Pending, Abandoned)  Date of Filing  Status (Patented, Pending, Abandoned)  Date of Filing  Date of Filing  Status (Patented, Pending, Abandoned)  Date of Filing  Date of Filing  Status (Patented, Pending, Abandoned)  Date of Filing  Date of Filing  Status (Patented, Pending, Abandoned)  Date of Filing  Dat	Application Number  Date of Filing  Application Number  Application Number  Date of Filing  Application Number  Date of Filing  Application is not disclosed in the prior United States application of this application is not disclosed in the prior United States afternational application of the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is repatentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT Interning date of this application.  Application Number  Date of Filing  Status (Patented, Pending, Abandoned PCT Interning Application Number Date of Filing Status (Patented, Pending, Abandoned PCT Interning Application, Paragraph Ap	US	09/060 756	16/04/1998	_ Y	YES D NO
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thereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) or § 365(c) of any PCT International application(s) designating the ited States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT menational application(s) in the manner provided by the first paragraph of 35 U.S.C. § 112, lacknowledge the duty to disclosed information which is material patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application(s) and the national or PCT International ng date of this application.  Application Number  Date of Filing  Status (Patented, Pending, Abandoned)  hereby appoint the following attorney and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected enewth. FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P., Douglas B. Henderson, Reg. No. 20.2031; Ford F. Farabow, Jr., Reg. No. 15.003, Arthur S. Garrett, Reg. No. 20.2020. Laurence R. Hetter, Reg. No. 20.2033; Bruce C. Total Reg. No. 20.2033; Bruce C. Zotal Reg. No. 20.2033; Bruce D. Larry Rourke, Reg. No. 20.2035. Herbert H. Minth, Reg. No. 20.2069; No. 20.2033; Bruce C. Zotaler, Reg. No. 20.2034; Subard D. Bartsky, Reg. No. 20.2033; Bruce C. Zotaler, Reg. No. 20.2034; B	hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) or § 365(c) of any PCT International application(s) designat inted States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States of emational application(s) in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is materiability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application(s) and the national or PCT Internated and the prior application.  Application Number  Date of Filing  Status (Patented, Pending, Abandoned Port International Po	hereby claim the benefit under 35 U.S	S.C. § 119(e) of any United States	provisional application(s) list	ted below:	
hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) or § 365(c) of any PCT International application(s) designating the inted States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT emational application(s) in the manner provided by the first paragraph of 35 U.S.C. § 112, 1 acknowledge the duty to disclose information which is material patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application(s) and the national or PCT International ng date of this application.  Application Number  Date of Filing  Status (Patented, Pending, Abandoned)  Patents in International Patents and Trademark Office connected eleventh, FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P., Douglas B. Henderson, Reg. No. 20.231; Ford F. Farabow, Jr., Reg. No. 20.302, pp. 10, 20.303, pp. 10, 20.3	hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) or § 365(c) of any PCT International application(s) designat itted States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States of emational application(s) in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is materially as defined in 37 CFR § 1.56 which became available between the filing date of the prior application(s) and the national or PCT International papers of this application.  Application Number  Date of Filing  Status (Patented, Pending, Abandone)  Intereby appoint the following attorney and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office conferent in the Finness of the prior application of the prior application of the prior application of the prior application.  Application Number  Date of Filing  Status (Patented, Pending, Abandone)  Intereby appoint the following attorney and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office conferent in the Filing of the prior application of th	Application N	Number		Date of Filing	
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inted States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCI emailtonal application(s) in the manner provided by the first paragraph of 35 U.S.C. § 112, lacknowledge the duty to disclose information which is material patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application(s) and the national or PCT International ng date of this application.  Application Number  Date of Filling  Status (Patented, Pending, Abandoned)  Interest, Pending, Abandoned)  Interest, Pending, Abandoned, PCT International patents, Pending, Pending, Abandoned, PCT International ng date of this application.  Application Number  Date of Filling  Status (Patented, Pending, Abandoned)  Interest, Pending, Abandoned)  Interest, Pending, Abandoned, PCT International PCT International ng date of the prior application(s) and the national or PCT International patents, PCT International ng date of the prior application (s) and the national or PCT International patents and patents and patents and patents are provided by the prior application (s) and the national or PCT International patents are provided by the prior application (s) and the national or PCT International patents are provided by the prior application (s) and the national or PCT International patents are provided by the prior application (s) and the national or PCT International patents are provided by the prior application (s) and the national or PCT International patents are provided by the prior application (s) and the national or PCT International patents are provided by the prior application (s) and the national or PCT International patents are prior application (s) and the national or PCT International patents are prior application (s) and the national patents and patents are prior applications in the prior application (s) and the prior application or PCT International patents and patents are prior application (s) and the prior applic	inted States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States of emational application(s) in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is materially as defined in 37 CFR § 1.56 which became available between the filing date of the prior application(s) and the national or PCT Interning date of this application.  Application Number  Date of Filing  Status (Patented, Pending, Abandoned PCT Interning date of the prior application (s) and the national or PCT Interning date of this application.  Application Number  Date of Filing  Status (Patented, Pending, Abandoned PCT Interning date of the prior application (s) and the national or PCT Interning date of this application.  Application Number  Date of Filing  Status (Patented, Pending, Abandoned PCT Interning date of the prior application (s) and the national or PCT Interning date of the prior application.  Application Number  Date of Filing  Status (Patented, Pending, Abandoned PCT Interning date of the prior application (s) and the national or PCT Interning date of the prior application.  Application Number  Date of Filing  Status (Patented, Pending, Abandoned PCT Interning date of the prior application (s) and the national or PCT Interning date of the prior application.  Application Number  Date of Filing  Status (Patented, Pending, Abandoned PCT Interning date of the prior application.) and the national or PCT Interning date of the prior application.  Application Number  Date of Filing  Status (Patented, Pending, Abandoned PCT Interning date of the prior application.) and the national or PCT Interning date of the prior application.  Application Number  Date of Filing  Status (Patented, Pending, Abandoned PCT Interning date of the prior application.) and the national or PCT Interning date of the prior application.  Application Number  Date of Filing date of the prior application.  Application Number  Date o			1		
Brewith, FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P., Douglas B. Henderson, Reg. No. 20,291; Ford F. Farabow, Jr., Reg. No. 630, Arthur S. Garrett, Reg. No. 23,38; Donald R. Dunner, Reg. No. 19,073; Brian G. Brunsvold, Reg. No. 22,593; Tipton D. Jennings, IV, Reg. No. 20,645; Bry D. Voight, Reg. No. 23,020; Laurence R. Hefter, Reg. No. 20,627; Kenneth E. Payne, Reg. No. 23,098; Herbert H. Mintz, Reg. No. 26,694; C. Larry Rourke, Reg. No. 26,014; Albert J. Santorelli, Reg. No. 22,640; Michael C. Elmer, Reg. No. 25,857; Richard H. Smith, Reg. No. 20,609; Stephen L. Peterson, eg. No. 28,325; John M. Romary, Reg. No. 26,331; Bruce C. Zotter, Reg. No. 27,680; Dennis P. O'Reilley, Reg. No. 27,932; Allen M. Sokal, Reg. No. 26,695; obert D. Bajefsky, Reg. No. 28,165; Thomas H. Srichard L. Stroup, Reg. No. 28,478; David W. Hill, Reg. No. 28,220; Thomas L. Irving, Reg. No. 28,619; Charles E. psey, Reg. No. 28,165; Thomas W. Winland, Reg. No. 27,605; Basil J. Lewris, Reg. No. 28,818; Martin I. Fuchs, Reg. No. 28,508; E. Robert Yoches, Reg. No. 30,157; Robert E. Converse, Jr., Reg. No. 27,432; Clair X. Mullen, Jr., Reg. No. 30,907; Richard B. Racine, Reg. No. 30,415; Thomas H. Jenkins, Reg. No. 30,853; Renneth J. Meyers, Reg. No. 25,146; Carol P. Einaudi, Reg. No. 32,220; Walter Boyd, Jr., Reg. No. 31,738; Sieven M. Anzalone, Reg. No. 30,953; Kenneth J. Meyers, Reg. No. 25,146; Carol P. Einaudi, Reg. No. 32,220; Walter Boyd, Jr., Reg. No. 31,964; Richard V. Burgujian, Reg. No. 31,744; J. Michael Jakes, Reg. No. 32,842; Barbara C. McCurdy, Reg. No. 32,220; Walter Boyd, Jr., Reg. No. 31,964; Richard V. Burgujian, Reg. No. 31,744; J. Michael Jakes, Reg. No. 32,284; Barbara C. McCurdy, Reg. No. 32,600; Thomas W. Banks, eg. No. 32,719; Christopher P. Isaac, Reg. No. 32,616; Bryan C. Diner, Reg. No. 32,697; David S. Forman, Reg. No. 33,694; Vincent P. Kovalick, Reg. No. 33,251; Charles E. Van Hom, Reg. No. 40,266; and No. 10,000; Thomas N. Reg. No. 33,694; Vincent P. Kovalick, Reg. No. 33,517; Winder Reg. No. 33,694;	erewith. FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P., Douglas B. Henderson, Reg. No. 20,291; Ford F. Farabow, Jr., K. 630; Arthur S. Garrett, Reg. No. 20,338; Donald R. Dunner, Reg. No. 19,073; Brian G. Brunsvold, Reg. No. 22,593; Tipton D. Jennings, IV, Reg. No. 20,827; Kenneth E. Payne, Reg. No. 23,098; Herbert H. Mintz, Reg. No. 26,691; C. Rourke, Reg. No. 26,014; Albert J. Santorelli, Reg. No. 22,610; Michael C. Elmer, Reg. No. 25,857; Richard H. Smith, Reg. No. 20,609; Stephen L. Peg. No. 26,325; John M. Romary, Reg. No. 26,331; Bruce C. Zotter, Reg. No. 27,580; Dennis P. O'Reilley, Reg. No. 27,932; Allen M. Sokal, Reg. No. obert D. Bajefsky, Reg. No. 25,387; Richard L. Stroup, Reg. No. 28,478; David W. Hill, Reg. No. 28,220; Thomas L. Irving, Reg. No. 28,619; Chr. psey, Reg. No. 28,165; Thomas W. Winland, Reg. No. 27,505; Basil J. Lewris, Reg. No. 28,181; Martin I. Fuchs, Reg. No. 28,508; E. Robert Yoche o. 30,120; Barry W. Graham, Reg. No. 29,924; Susan Haberman Griffen, Reg. No. 30,907; Richard B. Racine, Reg. No. 30,415; Thomas H. Jenkin o. 30,857; Robert E. Converse, Jr., Reg. No. 27,432; Clair X. Mullen, Jr., Reg. No. 20,348; Christopher P. Foley, Reg. No. 31,354; John C. Paul, R. 24,13; Roger D. Taylor, Reg. No. 28,992; David M. Kelly, Reg. No. 30,953; Kenneth J. Meyers, Reg. No. 25,146; Carol P. Einaudi, Reg. No. 32,220; Boyd, Jr., Reg. No. 31,738; Steven M. Anzalone, Reg. No. 32,995; Kenneth J. Meyers, Reg. No. 25,146; Carol P. Einaudi, Reg. No. 32,220; Boyd, Jr., Reg. No. 31,964; Richard V. Burgujian, Reg. No. 31,944; J. Michael Jakes, Reg. No. 32,984; Barbara C. McCurdy, Reg. No. 32,600; Thomas W. eg. No. 32,719; Christopher P. Isaac, Reg. No. 32,616; Bryan C. Diner, Reg. No. 32,409; M. Paul Barker, Reg. No. 32,013; Andrew Chanho Sonu, R. 3457; David S. Forman, Reg. No. 33,694; Vincent P. Koyalick, Reg. No. 32,867; James W. Edmondson, Reg. No. 33,871; Michael R. McGurk, R.	hereby claim the benefit under 35 U.S.0 ited States, listed below and, insofar a emational application(s) in the manner p patentability as defined in 37 CFR § 1.5	as the subject matter of each of the provided by the first paragraph of 35	ie claims of this application i 5 U.S.C. § 112. I acknowledge	is not disclosed in the e the duty to disclose	he prior United States or PCT e information which is material
prewith, FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P., Douglas B. Henderson, Reg. No. 20,291; Ford F. Farabow, Jr., Reg. No. 2630; Arthur S. Garrett, Reg. No. 20,338; Donald R. Dunner, Reg. No. 19,073; Brian G. Brunsvold, Reg. No. 22,593; Tipton D. Jennings, IV, Reg. No. 20,645; irry D. Voight, Reg. No. 23,020; Laurence R. Hefter, Reg. No. 20,627; Kenneth E. Payne, Reg. No. 23,098; Herbert H. Mintz, Reg. No. 26,694; C. Larry Rourke, Reg. No. 26,014; Albert J. Santorelli, Reg. No. 22,640; Michael C. Elmer, Reg. No. 25,857; Richard H. Smith, Reg. No. 20,609; Stephen L. Peterson, eg. No. 28,325; John M. Romary, Reg. No. 26,331; Bruce C. Zotter, Reg. No. 27,680; Dennis P. O'Reilley, Reg. No. 27,932; Allen M. Sokal, Reg. No. 26,695; obert D. Bajefsky, Reg. No. 28,165; Thomas H. Srichard L. Stroup, Reg. No. 28,478; David W. Hill, Reg. No. 28,220; Thomas L. Irving, Reg. No. 28,619; Charles E. psey, Reg. No. 28,165; Thomas W. Winland, Reg. No. 27,605; Basil J. Lewris, Reg. No. 28,818; Martin I. Fuchs, Reg. No. 28,508; E. Robert Yoches, Reg. No. 30,157; Robert E. Converse, Jr., Reg. No. 27,432; Clair X. Mullen, Jr., Reg. No. 30,907; Richard B. Racine, Reg. No. 30,415; Thomas H. Jenkins, Reg. No. 30,455; Thomas H. Jenkins, Reg. No. 30,953; Kenneth J. Meyers, Reg. No. 25,146; Carol P. Einaudi, Reg. No. 32,220; Walter Boyd, Jr., Reg. No. 31,954; Richard V. Burgujian, Reg. No. 32,953; kenneth J. Meyers, Reg. No. 25,146; Carol P. Einaudi, Reg. No. 32,220; Walter Boyd, Jr., Reg. No. 31,954; Richard V. Burgujian, Reg. No. 31,744; J. Michael Jakes, Reg. No. 32,984; Barbara C. McCurdy, Reg. No. 32,210; James K. Barmmond, Reg. No. 31,954; Richard V. Burgujian, Reg. No. 31,744; J. Michael Jakes, Reg. No. 32,284; Barbara C. McCurdy, Reg. No. 32,600; Thomas W. Banks, eg. No. 32,502; David S. Forman, Reg. No. 33,694; Vincent P. Kovalick, Reg. No. 32,249; M. Paul Barker, Reg. No. 32,600; Thomas W. Banks, eg. No. 31,954; Richard V. Burgujian, Reg. No. 31,514; Cherien M. Pelase address all correspondence to No.600; Reg. No. 20	erewith. FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P., Douglas B. Henderson, Reg. No. 20,291; Ford F. Farabow, Jr., K. 630; Arthur S. Garrett, Reg. No. 20,338; Donald R. Dunner, Reg. No. 19,073; Brian G. Brunsvold, Reg. No. 22,593; Tipton D. Jennings, IV, Reg. No. 20,827; Kenneth E. Payne, Reg. No. 23,098; Herbert H. Mintz, Reg. No. 26,691; C. Rourke, Reg. No. 26,014; Albert J. Santorelli, Reg. No. 22,610; Michael C. Elmer, Reg. No. 25,857; Richard H. Smith, Reg. No. 20,609; Stephen L. Peg. No. 26,325; John M. Romary, Reg. No. 26,331; Bruce C. Zotter, Reg. No. 27,680; Dennis P. O'Reilley, Reg. No. 27,932; Allen M. Sokal, Reg. No. 28,478; David W. Hill, Reg. No. 28,220; Thomas L. Irving, Reg. No. 28,619; Chr. psey, Reg. No. 28,165; Thomas W. Winland, Reg. No. 27,605; Basil J. Lewris, Reg. No. 28,181; Martin I. Fuchs, Reg. No. 28,508; E. Robert Yoche o. 30,120; Barry W. Graham, Reg. No. 29,924; Susan Haberman Griffen, Reg. No. 30,907; Richard B. Racine, Reg. No. 30,415; Thomas H. Jenkin o. 30,857; Robert E. Converse, Jr., Reg. No. 27,432; Clair X. Mullen, Jr., Reg. No. 20,348; Christopher P. Foley, Reg. No. 31,354; John C. Paul, R. 2413; Roger D. Taylor, Reg. No. 28,992; David M. Kelly, Reg. No. 30,953; Kenneth J. Meyers, Reg. No. 25,146; Carol P. Einaudi, Reg. No. 32,220; Boyd, Jr., Reg. No. 31,738; Steven M. Anzalone, Reg. No. 32,095; Jean B. Fordis, Reg. No. 32,984; Barbara C. McCurdy, Reg. No. 32,120; Jaammond, Reg. No. 31,964; Richard V. Burgujian, Reg. No. 31,744; J. Michael Jakes, Reg. No. 32,984; Dirk D. Thomas, Reg. No. 32,600; Thomas W. eg. No. 32,616; Bryan C. Diner, Reg. No. 32,409; M. Paul Barker, Reg. No. 32,013; Andrew Chanho Sonu, Reg. No. 33,694; Vincent P. Kovalick, Reg. No. 32,867; James W. Edmondson, Reg. No. 33,871; Michael R. McGurk, Reg. No. 32,871; McCard.	hereby claim the benefit under 35 U.S.0 lited States, listed below and, insofar a ernational application(s) in the manner patentability as defined in 37 CFR § 1.5 ng date of this application.	as the subject matter of each of th provided by the first paragraph of 35 56 which became available betweer	re claims of this application is U.S.C. § 112, I acknowledgen the filing date of the prior ap	is not disclosed in the the duty to disclose pplication(s) and the	he prior United States or PCT e information which is material anational or PCT International
Full Name of First Inventor COLE Stewart Inventor's Signature Date Nov. 3, 2000  Citizenship	inda A. Wadler, Reg. No. 33,218; and Please address all corresponding process. Please address all corres	hereby claim the benefit under 35 U.S.( fited States, listed below and, insofar a emational application(s) in the manner p patentability as defined in 37 CFR § 1.5 ng date of this application.  Application Number	as the subject matter of each of the provided by the first paragraph of 35 56 which became available between the provided by the first paragraph of 35 between the provided by	the claims of this application is U.S.C. § 112, I acknowledged the filing date of the prior application of Filing	is not disclosed in the ethe duty to disclose pplication(s) and the Status (Patented these in the Patent and th	d, Pending, Abandoned)
Residence	Full Name of First Inventor.  Inventor's Signature 1 A Date x 2 C	hereby claim the benefit under 35 U.S. (ited States, listed below and, insofar a emational application(s) in the manner patentability as defined in 37 CFR § 1.5 ng date of this application.  Application Number  Application Num	as the subject matter of each of the provided by the first paragraph of 35 56 which became available between 57 which became available between 58 which between	of Filing   sis not disclosed in the ethe duty to disclose pplication(s) and the Status (Patented ness in the Patent and N. Reg. No. 20,291; No. 22,593; Tipton D. 3,098; Herbert H. Mirard H. Smith, Reg. No. 26; Thomas L. Irving I. Fuchs, Reg. No. 30,20; Thomas L. Irving I. Fuchs, Reg. No. 30,20; Thomas Reg. No. 30,20; Thomas, Reg. No. 30,20; Reg. No. 32,013; A. Reg. No. 32,01	d, Pending, Abandoned)  d, Pending, No. 20,645;  ntz, Reg. No. 26,691; C. Larry  do, 20,609; Stephen L. Peterson,  dllen M. Sokal, Reg. No. 26,695;  g, Reg. No. 28,619; Charles E.  8,508; E. Robert Yoches, Reg.  8,508; E. Robert Yoches, Reg.  1,354; John C. Paul, Reg. No.  1,3	
		hereby claim the benefit under 35 U.S. (inted States, listed below and, insofar a emational application(s) in the manner patentability as defined in 37 CFR § 1.5 ng date of this application.  Application Number  Application Nu	Date  Ind/or agent(s) to prosecute this apparation of the provided by the first paragraph of 35 to which became available betweer between the provided by the first paragraph of 35 to which became available betweer between the provided by	of Filing   sis not disclosed in the ethe duty to disclose pplication(s) and the Status (Patented ness in the Patent and N. Reg. No. 20,291; No. 22,593; Tipton D. 3,098; Herbert H. Mirard H. Smith, Reg. No. 26; Thomas L. Irving I. Fuchs, Reg. No. 30,20; Thomas L. Irving I. Fuchs, Reg. No. 30,20; Thomas Reg. No. 30,20; Thomas, Reg. No. 30,20; Reg. No. 32,013; A. Reg. No. 32,01	d, Pending, Abandoned)  and Trademark Office connected Ford F. Farabow, Jr., Reg. No. Jennings, IV, Reg. No. 26,691; C. Larry D. 20,609; Stephen L. Peterson, Illen M. Sokal, Reg. No. 26,695; Reg. No. 28,619; Charles E. R. 196; Charles E. 197; Charles E. 198; Charles E. 199; Charles E.	

Listing of Inventors Continued on Page 2 hereof. 

Yes No

		Attorney Docket No	<u> </u>
isting of Inventors Continued From Page 1 hereof.			
Full Name of Second Inventor 2-00 BUCHRIESER-BROSCH Roland	Inventor's Signature	1-147	Date Nov. 3, 2000
Residence 75014 PARIS FRANCE	New address: 11 r		Citizenship AT
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Post Office Address 7 F boulevard Jourds	an	IK '	
Full Name of Third Inventor 3-00 GORDON Stephen	Inventor's Signature	Jednen Guden	Date Nov. 3, 2000
Residence 75015 PARIS, FRANCE	New address: 48 E Surey GU3 3BB / U	Broadacres, <u>Guilford</u> United Kingdom	Citizenship IE
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Full Name of Fourth Inventor 4-00 BILLAULT Alain	Inventor's Signature	Silland	Date Nov. 3, 2000
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Full Name of Fifth Inventor	Inventor's Signature		Date
Residence			Citizenship
Post Office Address			
Full Name of Sixth Inventor	Inventor's Signature		Date
Residence			Citizenship
Post Office Address			
Full Name of Seventh Inventor	Inventor's Signature		Date
Residence			Citizenship
Post Office Address			
Full Name of Eighth Inventor	Inventor's Signature		Date
Residence			Citizenship
Post Office Address			
Full Name of Ninth Inventor	Inventor's Signature		Date
Residence			Citizenship
Post Office Address			
Full Name of Tenth Inventor	Inventor's Signature		Date
Residence			Citizenship
Post Office Address			

SEQUENCE LISTING

1

į	1	GENERAL.	INFORMATION:
١	ı	) GENEKAN	TIME OTHER TENT

1	( i '	APPLICANT:

- (A) NAME: INSTITUT PASTEUR
- (B) STREET: 28 RUE DU DOCTEUR ROUX
- (C) CITY: PARIS CEDEX 15
- (E) COUNTRY: FRANCE
- (F) POSTAL CODE (ZIP): 75724
- (ii) TITLE OF INVENTION: A METHOD FOR ISOLATING A POLYNUCLEOTIDE OF INTEREST FROM THE GENOME OF A MYCOBACTERIUM USING A BAC-BASED DNA LIBRARY. APPLICATION TO THE DETECTION OF MYCOBACTERIA.
- (iii) NUMBER OF SEQUENCES: 5
  - (iv) COMPUTER READABLE FORM:
    - (A) MEDIUM TYPE: Floppy disk
    - (B) COMPUTER: IBM PC compatible
    - (C) OPERATING SYSTEM: PC-DOS/MS-DOS
    - (D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (EPO)
- (2) INFORMATION FOR SEQ ID NO: 1:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 12732 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: DNA (genomic)
  - (iii) HYPOTHETICAL: NO
  - (iv) ANTI-SENSE: NO
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

ACCTGCGCTT	GCAGAGATCA	AATAGGGCGC	ATGGGTCAGC	ATAGTACAGG	TCGTCGCGCA	60
TCTTTGATGC	ATCGGAATAA	GATGTCAGGC	AATTAAAAGA	GAAGCCACGG	CGACTCGCGG	120
CATTCAGCAT	GTCGAGCGTC	GCTTCGATGT	GAGCGCACCA	TTCCGTGTCC	AACGATTTCA	180
GACGAACATT	GAATATTCCA	CTCGCGACGC	TATAGTCCGC	CTCCCGATCT	ATGCGCGCCG	240
CGCAGATGAA	GTCTGCGTTC	GCCCGACCTT	CGAAACGTAG	TGCGGCCGCG	CGCACCATTT	300
CGGGGGAGAC	GTCGATGCCG	GTGTAATCAG	TTTTGAAGCC	ACGCGCATCT	AGGTAGTCCA	360
GTAGAGCCCC	ATAGCCACAG	CCTAGATCGT	TGATCGAAAA	TGGGTCCGCC	GCATTGACAA	420
TGCGCACCAG	CTGGTCAAAG	CGCAACGCCT	GCCCGGCTTC	GCCGTTCCAA	TCGACGCCGC	480
GCGGGTGCCG	TGTGCTTCGA	GTTTCGATGC	GTAGTAACGG	GCCACGTCAG	CGAGCATGGT	540

CGTTGCGTCT	TCCGCCATGA	AGCTGCCTCA	CGATTTGTGT	GTGTGGGCGT	CGGTGCGTGG	600
GTCCGAGACT	ATACCTTCAA	CAGTTGCATG	CCGAGGCTGC	GGCGGGCAAT	GACCCAAAAA	660
CCCGCCGGCA	CGGTTCGCCG	AGCAAGGAAG	CGTGGAGACG	ATAGATAATT	TCACTGGCGA	720
CAGTACCTCA	AATAGTCCGG	AGCCTCGGCT	CCGACGTTAA	AGAGCAGATC	CAGAATCGAC	780
ACGGCGGCT	CGAACCCTCC	CCACAATTGC	TTATAATCGC	GGTAGCCGTC	ATAATCGAAC	840
CAAGTTACCC	GGATGCTAAG	TTCGTCGAAC	ACGCGCTCAT	CGACATACGA	ACGGGCTGAG	900
GGGCCAGAGA	CATATTCGGT	CGCTGCGGCC	TGTTGGCAGA	GGTTGGCCAG	TCTCTCGGTC	960
TTGCCGTCGG	CTAATTCGTA	GTCCCACGAA	TTTGCCAGTC	GCGTGCTGAT	ACCGAGATAA	1020
CTGCAAATCG	CATTCAATAG	ACGCCTGTTG	AGTAAGGAAA	GATTCGTGTG	CTGTTCTTCG	1080
AGGTAAATCG	GCGCGAGCCA	GTCAGCGATC	TCCGCAAAAT	GAGCGGCCGC	GCTGTAGTTG	1140
AATTCTAGTG	CCCGCCAGTG	CGCTTTCGCC	CAATCGGTGC	CGTCGATCAG	CGTCTCACGT	1200
ATCTTTTGAT	GGAAACGTCC	CTTCACCTGG	ACGGGAACAG	TTATCCACTG	TAACCCCTGG	1260
CTCGTTTTGA	TCCGATTTCT	GTTTCGCCAA	TCACGCTTGG	TATATTGCAT	GTCATCATAG	1320
ATGATGAATT	CATCGACGAA	TGCAATCAGG	TCAAAATATC	CTCGCCAAGG	TATGTAATTT	1380
GATTGAACAA	TCGCGACTTT	CTTCAACGCG	GTGTCTCCAA	TTTAGAATAA	CAAATACGTC	1440
GCGCCCGCGA	CAGCTCCGCT	GGAGCGAGTT	CAAGCGATTC	TGCGACATAT	TCAATATGGT	1500
GCTCGGGAAG	GCCAGGATGG	GCCGCGACCC	GGGGCGTCCG	GTGCGCGATG	AACGTCGCAT	1560
CGTCTCCTGT	GAGATAATTG	CATCCGATCA	TATAGGGCTG	GCTGCGGCTA	GGTTGCTGGC	1620
AAAAAGATAT	CGCGGCCGAT	CCGTTTCTGG	TTTTGTCTTG	ATGATCAAAT	CCGCTTCCGT	1680
TCACGAGATC	GATTCCTGGT	CTTCCCCCAG	CGTCGCGATG	TCGATAGGT	TCGCGCTTTG	1740
TTCGTACCCG	CACTACGCGG	CGGCGAGAAC	CTCGCCACCG	AATCGGGATT	r GGGGGGAGGA	1800
TACCACTCGG	TCGAGGCCCG	TCACCGGCCT	TCTAGCGGGT	TGACCATCAC	TGTTTGCAGG	1860
GCCCTATCCC	GGTATGGCGC	CACCACGGGAT	CGGCAGCGTT	CCGGTTGCT	G GCGTGGTACC	1920
TCGTTGTGGC	GCCGTGGTC	ATGTCGATTC	AGTGCGTGG	A TCAGTGTAA	A CCGTTGCGCG	1980
CCATGTTCTC	TAGGCACTGG	G TTCGGGTTGT	T GGTTAGGCT	G CACGGTTGG	C AGGTTACCAA	2040
CCACTGAGC	C CCTGGGCGG	A TGTGAGCTC	G GACTCCGCC	r atggggtgt.	A ATTTTGGCAG	2100
ATTGGGCCG	G GTCCCCGTG(	G TGAGGACTC	C TCAACCGGA	r TGGGTAAGC	A TGAGGTGGTG	2160
CTGGCAGCG	G TGTCCTGGT	C GCTCTCCCG	A GTAGGCCCG	T TGTGACTGT	C ATGTGGGCGA	2220
	GTCCGAGACT CCCGCCGGCA CAGTACCTCA ACGGCGGGCT CAAGTTACCC GGGCCAGAGA TTGCCGTCGG AGTAATCG AGTAATCG AATTCTAGTG ATCTTTGAT CTCGTTTTGA ATGATGAACAA GCGCCCGCGA GCTCGGGAAG CGTCTCCTGT AAAAAGATAT TCACGAGATC TTCGTACCCG GCCTATCCC TCGTTGTGGCCCCCCCCCC	GTCCGAGACT ATACCTTCAA  CCCGCCGGCA CGGTTCGCCG  CAGTACCTCA AATAGTCCGG  ACGGCGGGCT CGAACCCTCC  CAAGTTACCC GGATGCTAAG  GGGCCAGAGA CATATTCGGT  TTGCCGTCGG CTAATTCGTA  CTGCAAATCG CATTCAATAG  AGGTAAATCG GCGCGAGCCA  AATTCTAGTG CCCGCCAGTG  ATCTTTTGAT GGAAACGTCC  CTCGTTTTGA TCCGATTTCT  ATGATGAATT CATCGACGAA  GATTGAACAA TCGCGACTTT  GCGCCCGCGA CAGCTCCGCT  GCTCGGGAAG GCCAGGATGG  CGTCTCCTGT GAGATAATTG  AAAAAGATAT CGCGGCCGAT  TCACGAGATC GATTCCTGGT  TTCGTACCCG CACTACGCGG  CCCTTTCCC GGTATGGCCC  CCATGTTCTG TAGGCACTCC  CCATGTTCTG TAGGCACTCC  CCATGTTCTG TAGGCACTCC  CCACTGAGCC CCTGGGCGGAT  ATTGGGCCGG GTCCCCGTGCC  CCACTGAGCC CCTTGGCCGCAT  ATTGGGCCGG GTCCCCGTGCCCC  CCACTGAGCC CCTTGGCCGCAT  CCACTGAGCC CCTTGGCCGCAT  ATTGGGCCGG GTCCCCGTGCCCCC  CCACTGAGCC CCTTGGGCGGATCCCCCCCCCCCCCCCCC	GTCCGAGACT ATACCTTCAA CAGTTGCATG CCCGCCGGCA CGGTTCGCCG AGCAAGGAAG CAGTACCTCA AATAGTCCGG AGCCTCGGCT ACGGCGGGCT CGAACCCTCC CCACAATTGC CAAGTTACCC GGATGCTAAG TTCGTCGAAC GGGCCAGAGA CATATTCGGT CGCTGCGGCC TTGCCGTCGG CTAATTCGTA GTCCCACGAA ACGCTAAATCG CATTCAATAG ACGCCTGTTG AGGTAAATCG CCGCCAGTG CGCTTCGCC AATTCTAGTG CCCGCCAGTG CGCTTCGCC ATCTTTTGAT GGAAACGTCC CTTCACCTGG CTCGTTTTGA TCCGATTCT GTTTCGCCAA ATGATGAATT CATCGACGAA TGCAATCAGG GATTGAACAA TCGCGACTT CTTCAACGCG GCGCCCGCGA CAGCTCCCT GGAGCGACCC CGTCTCCTGT GAGATAATTG CATCCGATCA AAAAAGATAT CGCGGCCGAT CCGTTTCTGG TCACGAGATC GATTCCTGGT CTTCCCCCAG TTCGTACCCG CACTACGCGG CGGCGAGAAC TCCGTTTCGC CACTACGCGG CGGCGAGAAC TCGTTGGGC GCCGTGGTCC ATGTCGATTC CCATGTTCTG TAGGCACTGG TCACCGGGCTG CCCATGTCCTG TAGGCACTGG TTCGGGTTCC CCACTGAGCC CCTGGGCCGA TCTCGGGTTCC ATTCGGGCCGG GTCCCGTGG TCCACGGGCTC CCACTGAGCC CCTGGGCCGA TCTCGGGTTCC CCACTGAGCC CCTGGGCCGA TCTCACGGCCC CCTGGGCCGG TTCACCGGCCG CCTGGCCGGA TCTCACGGCCC CCTGGCCGGA TCTCGGGTTCC CTATCCC CGCCTGGCCGA TCTCACGGCCCC CTGGGCCGGA TCTCCGCGCGA TCTCCGCCCGCGA TCTCCCCCGCGCGA TCTCCCCCGCGCGA TCTCCCCCGCGCGA TCTCCCCCGCGCGA TCTCCCCCGCGCGA TCTCCCCCGCGCGA TCTCCCCCGCGCGA TCTCCCCCGCGCA TCTCCCCCGCGCA TCTCCCCCGCGCA TCTCCCCCCGCGCA TCTCCCCCCGCGA TCTCCCCCCGCGA TCTCCCCCCGCGCA TCTCCCCCCGCCGCA TCTCCCCCCCCCC	GTCCGAGACT ATACCTTCAA CAGTTGCATG CCGAGGCTGC CCGCCGGGCA CGGTTCGCCG AGCAAGGAAG CGTGGAGACG CAGTACCTCA AATAGTCCGG AGCCTCGGCT CCGACGTTAA ACGGCGGGGCT CGAACCCTCC CCACAATTGC TTATAATCGC CAAGTTACCC GGATGCTAAG TTCGTCGAAC ACGCGCTCAT GGGCCAGAGA CATATTCGGT CGCTGCGGCC TGTTGGCAGA TTGCCGTCGG CTAATTCGTA GTCCCACGAA TTTGCCAGTC CTGCAAATCG CATTCAATAG ACGCCTGTTG AGTAAGGAAA AGGTAAATCG CCGCCAGGT CGCTTTCGCC CAATCGGTGC AATTCTAGTG CCCGCCAGTG CGCTTTCGCC CAATCGGTGC CTCGTTTTGA TCCGATTCT GTTTCGCCAA TCACGGTTGG ATGATGAATT CATCGACGAA TGCAATCAGG TCAAAATATC GATTGAACAA TCGCGACTT CTTCAACGG GTGTCTCCAA GCGCCCGCGA CAGCTCCGCT GGAGCGAGTT CAAGCGATTC GCTCGGGAAG GCCAGGATGG GCCGGAGCCC GGGGCGTCCG CGTCTCCTGT GAGATAATTG CATCCGATCA TATAGGGCTGG 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CTTCACCTGG ACGGGAACAG TTATCCACTG CTCGTTTTGAT GCAAACGTCC CTTCACCTGG ACGGGAACAG TTATCCACTG CTCGTTTTGAT TCACCAGAA TGCAATCAGG TCAAAATATC CTCGCCAAGG GATTGAAATT CATCGACGAA TGCAATCAGG TCAAAAATATC CTCGCCAAGG GATTGAACAA TCGCGACTTT CTTCAACCGG GTGTCTCCAA TTAAGAATAAA GCGCCCGCGA CAGCTCCGCT GGAGCGATC CAAGCGATC TGCGCAAGG GCTCCGGGAG GCCAGGATG GCCGCGACCC GGGGCGTCCG GTGCGCGATCA GCTCCGTTTTGA CGGGCCGATC CGTTTCTGC TTTTTGCACTG TTCAACAGA TCCGGACTTT CTTCAACCGC GTGTCTCCAA TTAAGAATAAA CCGCCCGCGA CAGCTCCGCT GGAGCGATCC GGGGCGTCCG GTGCGCGATC GCTCCCTGT GAGATAATTG CATCCGATCA TATAGGGCTG GCTGCGGATC TCACCAGGAT CCGTTTCTGG TTTTTTTTTTTT ATGAATAAA TCACCAGGATC GATTCCTGGT CTTCCCCCAG CGTCGCGATC TCGATAGGGT TTCGTACCCG CACTACGCGG CGGCGAACAC CTCGCCACC AATCGGGAT TTCGTACCCG CACTACGCGG CGGCGAGAAC CTCGCCACC AATCGGGAT TCCATTCCC GGTTTGGCG TCACCGGGAT CGGCAGCGT TCCACTCGGT TCCTTTCCC GGTTTGCCC ACCACGGAT CCGGTTGCT TCCTTTCCT TCAGGGCC TCACCGGCCT TCTAGCGGGT TCCACTGATCAC CCCCTATCCC GGTATGGCGC ACCACGGATC CGGCAGCGT CCGGTTGCTC TCCTTCTTCT TAGGCACTGG TCCGCGTTT ACCACTGG TCACCGGCT TCTAGCGGGT TCCGGTTGCT CCATTGTCC CCCTGGCCGA TCCGGCTT CTTAGCGGGT TCCACTGTTCC CCATTGTCC GGTTTGCCC ACCGGGAT CGGCTGGCC TCCCTTCCTC TTAGGCGCC TCCACCG ACCCGGTTGCC CCATGTTCC GGTTGGCCC ACCCGGATC CGGCTTCCCCCAC ACCGGTTGCC CCATGTTCC GGTTGGCCC ACCCGGGAT CGGCTGGCCT ATGGGGTTC CCACTGAGCC CCTGGGCGA TCCGCCC ATGGGGTTC CCACTGAGCC CCTGGGCGA TCCGCCC ATGGGGTTC CCACTGAGCC CCTGGGCGA TCCGCCC ATGGGGTTC CCACTGAGCC CCTGGGCGA TCCGCCC ATGGGGTTC CCACTGGCCG TCCCCGCG TCCCCGCC TCCACCGACC ATGGGGTTC CCACTGGCCG TCCCCGTGG TCCCGCC TCCAC	CGTTGCGTCT TCCGCCATGA AGCTGCCTCA CGATTTGTG GTGTGGGGGT CGGTGCGTGGGGGGTGCGTGGGGGGTAT ATACCTTCAA CAGTTGCATG CCGAGGCTGC GGCGGGCAAT GACCCAAAAA CCCGCCGGGCA CGGTTCGCCG AGCAAGGAAG CGGTGGAGACG ATAGATAATT TCACTGGCGA CAGTACCTCA AATAGTCCGG AGCCCGGCTC CCACAATTGC TTATAATCCG GGTAGCCGC ATAAATCGAC CAGGTTACCC GGATGCTAAG TTCGTCGAAC ACGGCCTCAT CGACATACGA ACGGCTGAG GGGCCAGAGA CATATTCGGT CGCTGCACATTGC TGTTGGCAGA GGTTGCCAGAG CTTCTCGGTC TGTTCCAGAC CAGGTTACCC GGATGCTAAG ACGCCCTCAT CGACATACGA ACGGCTGAG GGGCCAGAGA CATATTCGGT CGCTGCACA TTTGCCAGTC CCACAATTG ACCGAGATAA CCACAGATACA ACGGCTGAG GGGCAGAGA CATATTCGGT CGCTGCTGT AGTAGGAAAA GATTCGTGT CTTTCTGGTC CATTCAATAG ACGCCTGTTG AGTAAGGAAA GATTCGTGT CTTTCTTCG AGGTAAATCG CCGCCAGAG GCCTGTTTGAC CCACACATAG ACGCCTGTT AGCACACAC CATTCAATAG ACGCCTGTTG AGTAAGGAAA GATTCGTGT CTTTCTTCG AGGTAAATCG CCGCCAGGT CCCTTTCGCC CAATCGGTGC CGTCGATCAG CGTCTCACGT ATTCTTTGAT GCAGCAGAT CCCCTCACCTG ACGGAACAG TTATCCACTG CCTCTCACGT ACCCCTGG ACGGAACAG TTATCCACTG ACCCCTGG ACGGAACAG TCACCCTGG TATATTGCAT GTCAATAGA ACGCCCTT GTTTCGCCAA TCACGCTTG TATATTGCAT GTCAATAAG ACGCCCTTT CTTCAACCAG TCAAAAAAAAA TCCCCAGAA TGCAATCAGG TCAAAAAAATATC CTCGCCAAGG TATGTAATTT CAATAAGGTT CTTCAACCAG TCAAAAAAAAAA

GCGGGTTTGC G	GCGCGTAGGA	GACGATGATT	ACTACGCACG	TGACCAACCA	CAAGAACGGT	2280
GCCCATGTCA (	CCGTGGTGAA	AACGAGTGGC	GTGGTACCGA	CTACCCCTTT	GGCTCCCAGC	2340
TGTCCATAGA (	GCGGCACGTA	GAACGGCTGG	CCCGGGACCG	CGACGTTGAC	GATGCTCAGC	2400
GCCACGGCCA 2	AACTCACGCA	GACGCCGACC	GCGCGGCGGC	GGTCTCCATG	GGCTGCGAGT	2460
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TGAATCCCGG	CGGCGGCGAC	CATGGCGTAG	G TCGCTGAAG	C AGTGCCGAC	C GATATTCATG	3420
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TACCACTGAC	TGAGGGCGTI	A CGCCGTCGC	C GCCGAAATC.	A CCGACGCCA	G CAGGATGGTG	3540
CCGAGCATGA	GGGTGCGCT	C GGATTGGGA	g CCGATCGCC	C AGAGCCGCT	C CCGGCTCGCG	3600
GTCACGGCAC	CGCGCAACA	C CTCCGGGGG	T CGCTTCATC	T GGATTCTCC	T CGGTTCTGCG	3660
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AGGATGAACO	CACAGCCAC	G CCCCGACGT	T ATGCCATGG	C GAAGAGCGA	C CGGCAGGAGC	3840
GGGAACCCAG	G TGAAGCGAG	C GCTCATCAC	C GGAATCACA	AG GACCGGACC	G CTCGTATCTC	3900
GCTAAGCTC	C CGCTGAAGG	G ATATGTGGC	C GCTGGTAG	CC CGGCCGAG	T CTATTTCTGC	3960

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GTCACACGTG	CGGGTGAGCT	TCGACGAACC	CGTGCACACC	GGTGACACCA	CCGGCATGGG	7380

ATCCATGCGA	CTGCTGGAAG	CCGTTCGGCT	CTCTCGGGTG	CACTGCCGCT	TCTATCAGGC	7440
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CCCGCGGTCA	CCGTATGGCG	CCGCCAAGGT	CTATTCGTAC	TGGGCGACCC	GCAATTATCG	7560
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CATCTGCTGC	CGGCACTCAT	CCGCCGCTAT	GACGAGGCCA	AAGCCAGTGG	CGCGCCCAAC	8700
GTGACCAACT	GGGGCACCGG	CACGCCCCGA	CGGGAGTTGC	TGCACGTCGA	CGACCTGGCG	8760
AGCGCATGCC	TGTATCTGCT	GGAACATTTC	GACGGGCCGA	CCCATGTCAA	CGTGGGAACC	8820
GGCATCGACC	ACACCATCGG	CGAGATCGCC	GAGATGGTCG	CCTCGGCGGT	AGGCTATAGC	8880
GGCGAAACCC	GCTGGGATCC	AAGCAAACCG	GACGGAACAC	CACGCAAACT	GCTGGATGTT	8940
TCGGTGCTAC	GGGAGGCGGG	ATGGCGGCCT	TCGATCGCGC	TGCGCGACGG	CATCGAGGCG	9000
ACGGTGGCGT	GGTATCGCGA	GCACGCGGGA	ACGGTTCGGC	AATGAGGCTG	GCCCGTCGCG	9060

CTCGGAACAT CTTGCGTCGC AACGGCATCG AGGTGTCGCG CTACTTTGCC GAACTGGACT	9120
GGGAACGCAA TTTCTTGCGC CAACTGCAAT CGCATCGGGT CAGTGCCGTG CTCGATGTCG	9180
GGGCCAATTC GGGGCAGTAC GCCAGGGGTC TGCGCGGCGC GGGCTTCGCG GGCCGCATCG	9240
TCTCGTTCGA GCCGCTGCCC GGGCCCTTTG CCGTCTTGCA GCGCAGCGCC TCCACGGACC	9300
CGTTGTGGGA ATGCCGGCGC TGTGCGCTGG GCGATGTCGA TGGAACCATC TCGATCAACG	9360
TCGCCGGCAA CGAGGGCGCC AGCAGTTCCG TCTTGCCGAT GTTGAAACGA CATCAGGACG	9420
CCTTTCCACC AGCCAACTAC GTGGGCGCCC AACGGGTGCC GATACATCGA CTCGATTCCG	9480
TGGCTGCAGA CGTTCTGCGG CCCAACGATA TTGCGTTCTT GAAGATCGAC GTTCAAGGAT	9540
TCGAGAAGCA GGTGATCGCG GGTGGCGATT CAACGGTGCA CGACCGATGC GTCGGCATGC	9600
AGCTCGAGCT GTCTTTCCAG CCGTTGTACG AGGGTGGCAT GCTCATCCGC GAGGCGCTCG	9660
ATCTCGTGGA TTCGTTGGGC TTTACGCTCT CGGGATTGCA ACCCGGTTTC ACCGACCCCC	9720
GCAACGGTCG AATGCTGCAG GCCGATGGCA TCTTCTTCCG GGGCAGCGAT TGACGCGCCG	9780
GCGCGTCAAT CTATTTCGAC ATTCGCGTGA AGACGTTTTC CCAGAATCGA CTGTTGTAGG	9840
CGTAGAACTC CCGGCCGCGT AGGTAGGCAT GTGATATTCG CCTTCCCCCG AACGGGTAGC	9900
GGCGATGAAG GTCGCCCATG CGGCGCAGAT CACCGAAGAC CGCGCTTGGT TCCCGGTGCG	9960
AGCCGACGCC CGTGGTGTCG AACTCGCACA GCACACCCG AATCGTGACC GGCTCGCATA	10020
CCAGCGCGC CCGCAATATG AATTCCTGGT CGGCGGCGAT CCCGAAATCA AGGTCGTAGC	10080
CACCGATCTT GGCCACCAGC GATGATCCGA AGAACGATGC TTGATGCGGA ACAACCTGCT	10140
TGCCGGCCAG GAATTTGCGC AGGCTGAAAG GTATCGGGCC GCGCACCCGA TCGAGCCCGA	10200
CGAGACGATC CATCCCGAAG CCCCACAATT CGGACACCGG TCCCTTGCCG GATAGCGCCT	10260
CCACGGCCTG GGCTACCACG TCGGGCCCGG AAAAACGATC GGCGGAGTGC AAGAACCACA	10320
ACAGATCACC CGATGCGTGC GCGATGCCCT GGTTCATCGC GTCGTACCGC CCGCCGTCGG	10380
GCTCGGACTG CCAATACGCG AAGCCTGGTT CACACCCGGA CAGGTATGCC ACCACGTCGT	10440
CGCCGCTGCC ACCGTCGATT ACGATGTGCT CGATGCGTCC CCGGTAGCGT TGCGCCCGCA	10500
CACTTTTCAC CGTGCGCTGC AACCCGTCGA GGTCGTTGAA CGAGATCGTT ATCACCGAGA	10560
CGGTCGGAGC AGACGTCACC GAGTTCCCCT AGGTTGCTGG CGGCGATTGT GGATCACCGG	10620
GTCTTGATAC CGATGAAGGT GCCTCGAAGA TTCGCCGCAT AGGAACCTCC GAGCAACGAC	10680
TCGGCGATGC TTGGTTCCAA GTTGTCGTAC TCCTCCATCA CCAGGTCGAC GCCGACGTCT	10740
TTGATGGCCT GAAGTAGGTG CTCGCGTTGA ATCCAGAATG ACCGGCGATT GTCCCAGGAC	10800

GCCCATTTTG CGGTGTCGCG CTGGCCAAAC GAGCGGTCGT CGGAAAACTC GGTAAACCAC	10860
CTACCGGGAA GTCCCTCATG TTCGGTGGGC GCCGAGAGCA TGAACTTCAC CGGCGCCGGC	10920
CGCCGCAGCA ACCGATCGGT CAATTGTCGT GCCGTCGTGG GCAACCGGAG CCATTTATCG	10980
CTCCGGTTGA TGATCGAGAA GTGCGTCTGG AGAATCAGCA GCTTGTTCGT TACCGACGAG	11040
AGGGTTTCCA GGTATTGCTT CGGATTCTCC AGGTGGTAGA AGAGGCCGCA GCAGAAGACG	11100
GTATCGAAGA GCCCGTGGTT GGCGATGTTG AGGGCGTTGT CGTGGACGAA CCGGAGATTC	11160
GGCAGGTTGG TCTTCGATTT GATGTAGTTG CAGGCCGCCA TGTTCAGCTC GCGAACCTCG	11220
ATCCCGAGGA CCTGAAATCC CATGCGCGCG AACCCGACCG CGTACCCGCC TTCCAAGCAG	11280
CCGACATCGG CCAGGCGTAG GTGGCTCTTG TCCCCGGGAA AGACGGTTTC CAGAATCCCG	11340
CGCGCCGAGA TGAACCAGGA CGATTCGTCT AACGTGCGCG AGGACTCCGG TATCGTCAAG	11400
GTTCCGTCGT CGAGGCGAAC GTTGTGGGCG GTGAATTGTA CCGCGCCGGC CGAATGTTCC	11460
TGTGCCATCA CTTGGTTAGC CCCTTCGGCT GGTCCTGGGT TTGTCGACAT GGTCAGGCTC	11520
GACAGCCGCG TCGGAGCCGG GAGGGCCACA CATCCACGAG CCCCCTGCGG CTCGGCGTCG	11580
CGGCGGCGAG CTTGCGCCAC TGGGTCTTGA GCCGCCGCGC GGGTGTCGCC CCGCGGTGCT	11640
GCAGCGCCAG CATGGCGATC CGGGGATGGC GCGCGATGGT TTCCTGCAGC GCGGCGCGCC	11700
CCTCCGGGCC TGGAACGTTG GCGATCTGGC GAAGGATCCA GTCGGCCATG ACGGCGATGA	11760
GCTCCTCGCG CGCGGGGTCT CCCGGGAACA GGTCGAGCAT CGCGTCAAAC GTCGCCGCAT	11820
GCCCCGGACC CTGCGTCAAC CAGAACTTTG GCGGGTCCAC CACCTGGTTG TGCCACATGC	11880
CTTGGGCGTG GCGGCGATAC ACGGCCATGG TGTCGGGCAA CATGGCGATG TCGCCATGCA	11940
CCGCGTGCCG GACGTGCAGA TACCAGTCCA GGGGCATGAC GTCGGCAGGA ATGTCGTCGT	12000
AGCGCTCGAG GCGACGGTAC ACGGCCGAGT TGGTCTGGAT GAAGTTCATC AAGATCAACG	12060
CATCCAGGCT CAAGTTGCCC CGCACCCGAA CCGGGGGGAA CTTCGAGTCC TTGGCATGGC	12120
CGTCCTCCCA TATCACTCGG ACGGGATGGA AGCACACCGT CGTCTTGGGG TGCCGGTCGA	12180
GGAATGCGAC CTGTTTGCTT AGCTTCAGCG GATCGATCCA GTAGTCGTCC GCCTCGCACA	12240
ACGCGACGTA CTCGCCGCGA GCGGCCGACA GGGCGCCGGT CAGGTTCCCA TTGAGGCCGA	12300
GGTTTTCGGT CCTGAAGATC GGCCGGAACA CGTGCGGGTA CCGCTCGGCG TACTCACGGA	12360
TGATCGCCGG GGTGGCATCG GTCGACGCGT CGTCGGCGAC GATGATCTCC ACCGGGAAGT	12420
CGGTTTGCTG GTCGAGAAAG CTGTCGAAGG CCTGACGGGC GTAGCCCGCC TGGTTGTGAG	12480

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TGGTCGAGAC GATGCTCACC TTGGGGCAAA GCTGGGGACT CACCGTCGGC CCTTTTCCTG 12540							
CGCGGCCGCA AGGGTATTGC GATGGCGAAC GTGAATCGCC TGTGCCCGCC GGCCGTCGGC 12600							
CGTCGTGGCC TGGTGGTCGG CGGACGTACG GCACACGCTG GCGAAGTATA GCGAGGGTGC 12660							
ACTGACGTTG GGCTCGAACC GCGTGGCGCG CGGTGTGGGC GCACCGTCTC GAGTCGGTGC 12720							
TGGTTGGCTC GC 12732							
(2) INFORMATION FOR SEQ ID NO: 2:							
<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 289 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>							
(ii) MOLECULE TYPE: DNA (genomic)							
(iii) HYPOTHETICAL: NO							
(iv) ANTI-SENSE: NO							
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:							
ATACTCAAGC TTGCCGCAAT CGAAACCAAC CTGTTTGTGC CGCAAGAAAT TACGCCGTGG 60							
CCCGGCGCG ATCAAGAAAC GCCCCGGCGC GCGGCGTGT CGTCGTATGG CATGACGGGC 120							
ACCAATGTGC ACGCCATTGT CGAGCAGGCA CCGGTGCCAG CCCCCGAATC CGGTGCACCA 180							
GGCGACACCC CGGCCACACC CGGTATCGAC GGCGCGCTGC TGTTCGCGCT GTCGGCCAGC 240							
TCGCAGGACG CGCTGCGGCA AACCGCCGCG CGGCTGGCCG ATTGGGTCT 289							
(2) INFORMATION FOR SEQ ID NO: 3:							
(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 278 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear							

- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) HYPOTHETICAL: NO
- (iv) ANTI-SENSE: NO
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

CTGGACTACC	CGCGTGGCCA	ATCTGCTGAA	CTCGCGGCCG	GTGGTGGCCT	GGAATGTCCA	240
CGCCGTTCAC	CTACGTGACC	TTGATGGGAT	CCGGGGGT			278

- (2) INFORMATION FOR SEQ ID NO: 4:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 1280 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: DNA (genomic)
  - (iii) HYPOTHETICAL: NO
  - (iv) ANTI-SENSE: NO
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

GGCGGGGGG GCTCGGGCGC GCCCGGCGG GCGGGGGGG CTGCCGGGCT GTGGGGTACC GGCGGGGCCG GCGGATCGG CGGAGCCAGC ACCGTACTCG GCGGCACCGG CGGGGAGGC GGGGTCGGTG GGCTGTGGGG CGCCGGTGGG GCCGGCGGGG CCGGTGGAAC CGGCCTTGTT GGTGGCGACC GCGGGCCGG TGGGGCCGGC GGGACCGGC GACTGCTGGC CGGCGTGATC GGTGCCGGCG GAGGTCACGG CGGAACCGGC GGGCTCAGCA CTAATGGCGA CGGCGGGTT GGCGGGGCCG GCGGAATGC CGGAATGCTC GCCGGGCCGG	
Gecegegece Getegearce Gecegegece Gecegegece Gecegegece Gecegearce	60
GGCGGGGCCG GCGGGATCGG CGGAGCCAGC ACCGTACTCG GCGGCACCGG CGGGGAGGC GGGGTCGGTG GGCTGTGGGG CGCCGGTGGG GCCGGCGGGG CCGGTGGAAC CGGCCTTGTT GGTGCCGGCG GCGGGGCCGG TGGGGCCGGC GGGACCGGCG GACTGCTGGC CGGGCTGATC GGTGCCGGCG GAGGTCACGG CGGGACCGGC GGGCTCAGCA CTAATGGCGA CGGCGGGTT GGCGGGGCCG GCGGAATGCC CGGAATGCTC GCCGGGCCGG	120
GGGGTCGGTG GGCTGTGGGG CGCCGGTGGG GCCGGCGGGG CCGGTGGAAC CGGCCTTGTT  GGTGCCGACG GCGGGGCCGG TGGGGCCGGC GGGACCGGCG GACTGCTGGC CGGGCTGATC  GGTGCCGGCG GAGGTCACGG CGGGACCGGC GGGCTCAGCA CTAATGGCGA CGGCGGGGTT  GGCGGGGCCG GCGGAATGCT GCCGGGCCGG GCGGCCCGG CGGAGCCGGC  GGTGACGGCG AAAACCTGGA CACCGGTGGG GACGGCGGG CCGGCGGTAG CGCAGGGCTG  CTGTTCGGCA GCGGCGGCG CGGCGGCGC GGCGGATTTG GTTTCCTCGG TGGGGACGGC  GGGGCCGGTG GCAACGCCGG GCTGCTGTTG TCCAGCGGCG GGCCCGGCG GTTCGGCGGG  TTCGGCACCG CCGGTGGGGT CGGTGGGGCC GGCGGCAATG CCGGCTGGCT GGGCTTCGGC  GGGGCCGGGG GCATCGGCGG AATCGGCGG AACGCTAACG GGGCCCCGG TGGGAACGGC  GGCACCGGCG GTCAGTTATG GGGTAGCGGC GGCGCCGGC TCGAAGGCGG CGCAGCCTTA  AGCGTCGGCG ACACCGGCGG GGCCGGTGGC GTCGGCGGCA GCGCCGGCT GATCGGCACC	180
GGTGGCGACG GCGGGGCCGG TGGGGCCGGC GGGACCGGCG GACTGCTGGC CGGGCTGATC GGTGCCGGCG GAGGTCACGG CGGGACCGGC GGGCTCAGCA CTAATGGCGA CGGCGGGGTT GGCGGGGCCG GCGGGAATGC CGGAATGCTC GCCGGGCCGG	240
GGTGCCGGCG GAGGTCACGG CGGGACCGGC GGGCTCAGCA CTAATGGCGA CGGCGGGGTT GGCGGGGCCG GCGGGAATGC CGGAATGCTC GCCGGGCCGG	300
GGCGGGGCCG GCGGGAATGC CGGAATGCTC GCCGGGCCGG	360
GGTGACGGCG AAAACCTGGA CACCGGTGGG GACGGCGGGG CCGGCGGTAG CGCAGGGCTG CTGTTCGGCA GCGGCGGCG CGGCGGCGC GGCGGATTTG GTTTCCTCGG TGGGGACGGC GGGGCCGGTG GCAACGCCGG GCTGCTGTTG TCCAGCGGCG GGGCCGGCGG GTTCGGCGGG TTCGGCACCG CCGGTGGGGT CGGTGGGGC GGCGGCAATG CCGGCTGGCT GGGCTTCGGC GGGGCCGGGG GCATCGGCGG AATCGGCGGT AACGCTAACG GGGCGCCGG TGGGAACGGC GGCACCGGCG GTCAGTTATG GGGTAGCGGC GGCGCGGCG TCGAAGGCGG CGCAGCCTTA AGCGTCGGCG ACACCGGCGG GGCCGGTGGC GTCGGCGGCA GCCCGGCCC GATCGGCACC	420
CTGTTCGGCA GCGGCGGCG CGGCGGCGC GGCGGATTTG GTTTCCTCGG TGGGGACGGC GGGGCCGGTG GCAACGCCGG GCTGCTGTTG TCCAGCGGCG GGGCCGGCGG GTTCGGCGGG TTCGGCACCG CCGGTGGGGT CGGTGGGGCC GGCGGCAATG CCGGCTGGCT GGGCTTCGGC GGGGCCGGGG GCATCGGCGG AATCGGCGGT AACGCTAACG GGGGCGCGG TGGGAACGGC GGCACCGGCG GTCAGTTATG GGGTAGCGGC GGCGCCGGCG TCGAAGGCGG CGCAGCCTTA AGCGTCGGCG ACACCGGCGG GGCCGGTGGC GTCGGCGGCA GCGCCGGCCC GATCGGCACC	480
GGGGCCGGTG GCAACGCCGG GCTGCTGTTG TCCAGCGGCG GGGCCGGCGG GTTCGGCGGG TTCGGCACCG CCGGTGGGGT CGGTGGGGCC GGCGGCAATG CCGGCTGGCT GGGCTTCGGC GGGGCCGGGG GCATCGGCGG AATCGGCGGT AACGCTAACG GGGGCGCCGG TGGGAACGGC GGCACCGGCG GTCAGTTATG GGGTAGCGGC GGCGCCGGCG TCGAAGGCGG CGCAGCCTTA AGCGTCGGCG ACACCGGCGG GGCCGGTGGC GTCGGCGGCA GCGCCGGCCT GATCGGCACC	540
TTCGGCACCG CCGGTGGGGT CGGTGGGGCC GGCGCAATG CCGGCTGGCT GGGCTTCGGC GGGGCCGGGG GCATCGGCGG AATCGGCGGT AACGCTAACG GGGGCGCCGG TGGGAACGGC GGCACCGGCG GTCAGTTATG GGGTAGCGGC GGCGCCGGCG TCGAAGGCGG CGCAGCCTTA AGCGTCGGCG ACACCGGCGG GGCCGGTGGC GTCGGCGGCA GCGCCGGGCT GATCGGCACC	600
GGGGCCGGGG GCATCGGCGG AATCGGCGGT AACGCTAACG GGGGCGCCGG TGGGAACGGC GGCACCGGCG GTCAGTTATG GGGTAGCGGC GGCGCCGGCG TCGAAGGCGG CGCAGCCTTA AGCGTCGGCG ACACCGGCGG GGCCGGTGGC GTCGGCGGCA GCGCCGGGCT GATCGGCACC	660
GGCACCGGCG GTCAGTTATG GGGTAGCGGC GGCGCCGGCG TCGAAGGCGG CGCAGCCTTA  AGCGTCGGCG ACACCGGCGG GGCCGGTGGC GTCGGCGGCA GCGCCGGGCT GATCGGCACC	720
AGCGTCGGCG ACACCGGCGG GGCCGGTGGC GTCGGCGGCA GCGCCGGGCT GATCGGCACC	780
	840
	900
GGCGGCAACG GCGCCACCGGC GCCAACGCCG GCAGCCCCGG AACCGGCGGC	960
GCCGGCGGGT TGCTGCTGGG CCAAAACGGG CTCAACGGGT TGCCGTAGCC GGGCGGCACG	1020
GCATGGCTTC CGGGCGTCAA CCACTCGCCG GTGATGCAGA TCGGCTGCGG AGCGGGCCGC	1080

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CGACACC

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CAAAATGGGG GCCGCCGCGC CAGGTATCTC GGCGAAGATC CCCGGCGCTC GAGCGCTTTG	1140						
TCAGAGGCCC GTCGCGGGTC GTCGTGACGA CGGCTATCCG GGCGGTGCGG GTTTCGCGGC	1200						
GCGCCCTGTG CCCGGCACCG CCGCCCGTTT GTCGGCAACG CCGCCGCGAC CCGTGAGCCG	1260						
TCCAGCAGCT GGCGCCTGCG	1280						
(2) INFORMATION FOR SEQ ID NO: 5:							
(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 127 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (iii) HYPOTHETICAL: NO  (iv) ANTI-SENSE: NO							
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:							
GGGCATCGGC GGAATCGGCG GTAACGCTAA CGGGGGCCCC GGTGGGAACG GCGGCACCGG	60						
CGGTCAGTTA TGGGGTAGCG GCGCGCCGG CGTCGAAGGC GGCGCAGCCT TAAGCGTCGG	120						